

Who Will be Responsible for Innovation?

THE National Research Development Corporation, which publishes its annual report this week (see page 184) is one of the many parts of the British Government's machinery for research and development that has been left in a kind of limbo by the most recent reorganization of publicly supported science. The White Paper on the research councils and other instruments of government policy which appeared in July (see *Nature*, **238**, 52; 1972) had nothing to say about the future of the corporation. And although it does appear that the Department of Trade and Industry has undertaken a review of the corporation's role, the chances are small that the outcome of this introspection will be a thorough reappraisal of the machinery which now exists for making sure that the fullest commercial use is made of the innovations thrown up by publicly supported research and development. The National Research Development Corporation, at least as it is at present constituted, can meet only a small part of the need.

The corporation owes its existence to the suspicion, in the years immediately after the Second World War, that British industry was slow to exploit many inventions which might be turned to profit. In its early years, the corporation threw open its doors to private inventors, but experience has shown that the bulk of its business comes from government departments, the research councils and the universities. This, of course, is no surprise, if only because private inventors must lead an increasingly marginal existence. At the beginning, it was intended that the corporation should eventually become a self-financing commercial operation, paying interest on the capital provided by the Treasury and using the profits from successful ventures to make good the losses from the failures there must inevitably be in such a chancy operation as the exploitation of innovation. For several years, the corporation used its income from the Bailey Bridge to keep its books more or less in balance. Now the antibiotic called cephalosporin is dominant among its money-spinners. Over the years, the corporation's capital has been increased to just under £25 million (and last year it paid out £1.78 million in interest to the Treasury). But in spite of support from the House of Commons for the view that the corporation should not be required to balance its books, in the most recent year of operations, there has even been a modest surplus. Financially, in other words, the National Research Development Corporation is beyond reproach.

So why not leave well alone? This is what the corporation's friends will say. The answer is that as it is at present constituted, the corporation can make only a marginal contribution to the task of exploiting effectively the innovations that stem, directly or otherwise, from public supported research and development. The latest list of projects taken on shows how miscellaneous are the projects which the corporation supports, that there are machines for harvesting blackcurrants, schemes for developing glass fibres resistant to alkalis, and a project

to develop an artificial knee. Nobody will deny the usefulness of this work, although there are reasons for thinking that the corporation might on many occasions have been better advised to ensure that there is a market for its products and a manufacturer willing to exploit it. And although the corporation has sponsored useful work in the development of various kinds (and has sometimes let its enthusiasm get the better of its commercial sense), it has found its ambitions in the development of computer systems restricted, quite understandably, to peripheral developments. Over the years, the corporation has quite properly sought to make agreements with industrial companies on the exploitation of new techniques (and the scheme for manufacturing protein from carbohydrates is a good example, for the commercial partner—Ranks Hovis McDougall Limited—is likely to be a vigorous exploiter of any benefits that may result) but in many of these circumstances, there is at least a case for asking whether it would not have been better to set up a direct relationship between the originating laboratory and the commercial enterprise. This, after all, is a pattern that seems to have worked well in some of the research and development carried out in the past few years at the Atomic Energy Research Establishment at Harwell.

The central question which the Department of Trade and Industry must ask itself is in any case much wider. What should be the scale on which government laboratories should seek to sponsor industrial innovation, and what relationship should there be between government laboratories and the industrial enterprises which might eventually profit? The first thing to be said is that these questions have in recent years been bedevilled by confusion about the proper use of public money. The British Civil Service differs from those of the United States and Japan in its conviction that public expenditure on research and development should never be allowed to find its way without recompense into the hands of industry. For this reason, the National Research Development Corporation has often been regarded as a welcome broker of innovations which stem from public research and development, and the requirement that it should balance its books, taking one year with another, is a measure of the Treasury's wish to see that public innovation is paid for. Anomalously, however, the Department of Trade and Industry then finds itself compelled to support areas of research and development which are reckoned to be of national importance by lending large sums of money to industrial concerns, as with the recent loan to International Computers Limited on terms much less favourable to the taxpayer than they should be.

In circumstances like these it is entirely understandable that the Government's intervention in important areas of industrial development should be limited to situations in which there seems to be a danger of disaster—the collapse of a crucial industry. In retrospect, it is ironical that for all the breast-beating of the past few years about the technical efficiency of the British machine tool industry,



the Government has not found a way of improving the competitiveness of this once important industry. It is hard to escape the conclusion that everybody would have been better off if the money spent on helping the industry with special purchases of machine tools had been spent instead in government laboratories on a programme of research and development agreed in advance with those companies within the industry willing to undertake the vigorous exploitation of anything that might result but without the payment of royalties. Where computers are concerned, it is still not too late to hope that the great government laboratories preoccupied with defence electronics should be set to work on the kind of research and development that might in due course make an efficient computer industry in Britain. The trouble is that such a programme would not merely offend the Treasury's belief in the sanctity of public money but that it also requires that the Department of Trade and Industry be equipped to make a much more hard-headed appraisal of the value of research and development than it is at present. And although there is no reason why the National Research and Development Corporation should not continue to exist, it is plainly time to recognize that it cannot make any useful contribution to the strategic developments now urgently needed.

Congressional Assessment

FOR close on a decade the United States Congress has modestly acknowledged its incapacity to settle complicated technical questions by the normal committee procedure and for much of that time it has been clamouring for some means of carrying out what is now called technology assessment. If there are no mistakes between now and the pre-election recess, Congress should at some point next year be provided with a form of apparatus for the evaluation of proposals for spending money on technological innovations of one kind or another (see page 186). The scheme for setting up a technology assessment unit, originally advocated by Mr Emilio Q. Daddario in his days as Chairman of the Sub-Committee on Science, Research and Development in the House of Representatives, has been improved as the years have drifted. It is entirely sensible that if there has to be such an organization, it should be equipped to commission studies from the many organizations in the United States, in universities and non-profit institutions, which have in the past few years become skilled at work like this. At the same time, however, Congress will be leading itself up the garden path if it thinks that technology assessment will do much to simplify the process of deciding whether new schemes for spending public money are free from the unanticipated side-effects which have made it fashionable, in Congress as well as outside, to suppose that technology has become a hazardous influence on society.

The recent history of the supersonic air-transport project should be a sufficiently vivid reminder. To begin with, the arguments against the spending of public money on the SST were largely economic. Was it right that the Administration and the Boeing Company should have settled for an aircraft designed to fly at three times the speed of sound and for all the technological complications, which that decision entailed—titanium alloys in

the aircraft skin and complicated joints for altering the attitude of the wings? And was it sensible, in any case, to think that airlines would equip themselves with such aircraft so soon after buying Jumbo jets and at a time (two years ago) when the growth of airline traffic appeared less buoyant than it had been and has since become? Senator William Proxmire did a useful public service in bringing out the uncertainties in the economic case for building SSTs, and it still remains a puzzle to know how the airlines proposed to turn round huge supersonic transports in just over an hour at the end of each leg of a journey. Undoubtedly it would have helped Congress if there had been an independent organization able to dissect the errors in the Administration's case, but it is hard to think that in a field where uncertainties are commonplace, such as this, any independent economic assessment would have satisfied the putative aircraft manufacturers and their sponsors in the government. It might have clarified the issues and made them sharper, but that is all.

Other objections to the SST project would have been as difficult for the Technology Assessment Panel to grapple with as other independent people have since discovered. How serious will be the effect of sonic booms? What precisely will be the effects on the upper atmosphere of large fleets of supersonic transports plying their way along the air routes of the world? Although there is now good reason to believe that predictions of serious consequences have been exaggerated, the proof of what the side-effects will be will come only several years from now, when supersonic aircraft are in regular service. So would the Technology Assessment Panel have had more to say than that there is an urgent need for more research? And would such a conclusion have affected the way in which Congressmen and Senators voted on the allocation of funds by the Administration? Is it not much more probable that the decisive influences would have been precisely what they turned out to be—political. No doubt the decision, just over a year ago, to abandon the SST project in the United States would have gone the other way if there had been more reason to think that either Concorde or the Tu144 would have been a serious threat to the international supremacy of American aircraft manufacturers. And it remains a fact that what Congress eventually decided stemmed as much from its wish to show the White House who was boss as from a belief in the judicial permanence of its decision.

Nature's Parish

ALL journals welcome a vigorous correspondence column, and *Nature* is no exception. Moreover, there is a sense in which uninhibited correspondence can enormously enhance the sense of community which journals and newspapers create among their readers and which, in the long run, is what they are for. In this spirit, it is entirely welcome that *Nature* should be used as a means of ventilating the accumulated grievances among British astronomers, which is why it is natural that Professor Burbidge's complaint two weeks ago about the organization of observational astronomy should have been published—and it is a little odd that so far it has evoked only the most muted (and verbal) comments. In exactly the same way, there is no doubt that comments on the

organization of, say, the scientific literature should find their way into the correspondence columns of a professional scientific paper. Similarly, there have been (and will no doubt be again) disputes about the exact weight to be given to documents such as *The Limits to Growth*, the Club of Rome's first encyclical. And any subject which seems proper as a topic for editorial comment is by definition fair game for those who wish to protest their disagreement—it would be intolerable if journals assumed for themselves a freedom they denied to their correspondents. To be sure, there are good reasons why journals should eschew public discussions of how they manage their domestic affairs (a frequent source of frustration for would-be correspondents in *Nature*), but that is not a serious cause of difficulty. With professional journals, however, there are constant difficulties in knowing where to draw the line between legitimate professional controversy and correspondence which seems to stray outside the bounds of what is seemly.

In the past few weeks, a number of correspondents have been asking why a journal which chooses to comment on the causes of, and the possible remedies for, the violence which led to the murder of Professor Aaron Katchalsky at Lod Airport earlier in the summer should not also comment on the conduct of the United States in south-east Asia. The short answer, which has since been challenged, is that the Vietnam war is "not part of *Nature's* parish" (see *Nature*, 238, 57; 1972). In this spirit, *Nature* has in the past few weeks declined to publish a moderate protest at the application of modern scientific techniques to the war in Vietnam which was drafted and signed by a distinguished group of scientists participating in the Varenna Summer School on the History of Physics. Some explanation of these decisions may be appropriate.

The first thing to be said is that there are important ways in which scientists, as professionals, can inform the making of public policy even in matters where political and military considerations are predominant. The history of the post-war world is an eloquent proof of that. It would have been intolerable if the testing of nuclear weapons in the atmosphere had not been recognized, on scientific grounds, as the indiscriminate hazard to human health which, mercifully, it has now been recognized to be. Similarly, the scientific arguments against the continued development of chemical and biological weapons (among which the assertion that their military usefulness has been exaggerated may have been the most influential) have had a powerful and beneficial influence. Professional scientists, arguing as scientists, have helped powerfully to draw attention to the dangers of the continuing gap between the rich and poor nations of the world. And where Vietnam is concerned, the arguments which have been levelled at the use of herbicides as military weapons are entirely proper, and seem also to have helped to moderate a thoughtless policy. Either by correspondence or by other means, it seems appropriate that a general scientific journal should take up cudgels in such a cause.

The difficulties arise with more general protests against the war in Vietnam. There are few who fail to curl with horror at the tales which have been brought back from places like My Lai but it is by no means self-evident that scientists are more affected than other groups of people, or that they have especially constructive safeguards to suggest against this kind of violence. May it not be that so long as there are wars, especially wars in which

armies fight on foreign soil, the risk of violence like this can never be reduced to zero? And although it may be true that the weapons now being used by the United States Air Force in the battles over south-east Asia are more sophisticated than older weapons, and dependent in their conception on recent developments in technology—lasers for example—can it be seriously held that the innovations of military technology are in themselves a cogent reason why the United States should now withdraw from its involvement in Vietnam? Is it not more likely that the political arguments against the folly of this enterprise which seem now to be widely accepted even in the United States are still the more forceful? And if that is so, is there not at least a case for asking that discussions of the course that should now be followed by the government of the United States should be informed by a proper appreciation of the political consequences that would follow from a radical change of policy? The difficulty, of course, is that *Nature*, like at least some of its correspondents, is not properly equipped to follow the ramifications of such tortuous matters. And if it were, it would be a journal of a different kind. None of this suggests that contributors and correspondents to *Nature* should refrain from drawing attention to new developments in technology which are likely to influence political and military events, and it would of course be news of professional importance if, for example, the Royal Society were to utter a ringing declaration against the Vietnam war, but it does seem proper to draw the parish boundary at the point at which political discussions are bound to be incomplete and, even half-baked.

100 Years Ago



So long as spectroscopic analysis is content to remain in its earliest stages—and it must be allowed to be still in its infancy, though a giant from its birth—the student and experimentalist may to a very considerable extent learn by heart or by practice such spectra as he needs; but this can never suffice for all purposes. Accumulation is continually going on, and products must be stored. Let that be once acknowledged and the task attempted, and it must follow that, no matter how rigorous and precise may be the system of tabulation, there will be not only room, not only gain, but a positive necessity for an intelligible use of that kind of descriptive indication which is only to be found in scientific classification and nomenclature.

A general catalogue such as I contemplate would command, if compiled with even moderate knowledge and care, a very general acceptance. Unquestionably it would be extended, modified, improved upon, by subsequent work; but, so far as nomenclature is concerned, it would probably undergo but slight alteration—the less the better. It would form a basis on which any number of special catalogues might rest, without interfering with its permanence as a catalogue of reference.

I do not pretend to say that the task is a simple one; quite the reverse. But, then, all the more honour to whoever accomplishes it.

J. HERSCHEL

Bangalore, July 29

From *Nature*, 6, 434, September 26, 1872.

OLD WORLD

Royal Commission in a Quandary

FEARS, some real some imaginary, of several members of the Royal Commission on Environmental Pollution have prevented the commission from recommending that polluters must pay for using estuaries and coastal waters as sinks for their wastes (Royal Commission on Environmental Pollution, Third Report, *Pollution in some British Estuaries and Coastal Waters* Cmnd. 5054, £0.85).

Sir Eric Ashby, chairman of the commission, said on Tuesday that all members of the commission agreed that the introduction of charges is one way of controlling pollution but only two members, Professor Wilfred Beckerman with no less an ally than Lord Zuckerman, recommended that such a system be introduced without delay to replace the present system of granting consent to any prospective water polluter.

Professor Beckerman said that he was convinced on two scores that such a system would work. First, he said, the time is now ripe, with the water services in Britain in the process of being re-organized, for the system to be introduced. Second, detailed economic justification for the successful operation of the price mechanism for controlling pollution is given by him in the report. Lord Zuckerman, while confessing that the economic arguments were not the all-convincing factors as far as he was concerned, said that any stimulus to abate pollution is good, and that if such a system were introduced, companies would find ways of making pollutants harmless instead of discharging them. The reservations of the other seven members of the commission about the immediate introduction of charges as a means to control pollution are as follows:

- Would charging companies for emitting waste have the same effect as the present system of granting consent to prospective polluters? In particular, would the new method, which "would put inducements and not obligations on industry" guarantee the same quality of water?

- Has Britain sufficient expertise to administer such a system? In particular, how will the charges for different stretches of water be decided, and once such a system is set up, will it put resources to their most efficient use?

- The political and social effects of a charging system must be considered before implementation. For example a charging system could favour companies which operate with a large profit margin over other companies and it will possibly favour industry over public

bodies.

Sir Eric, in introducing the report, pointed out that estuaries have so far been the cinderellas of pollution legislation and that they are at risk as companies will deposit their waste where there is least risk of prosecution and not where it will best be dispersed. Even though legislation will be introduced in 1974 which will give river authorities wider control than at present, the commission stresses that it will be ten years before the full effect of the new legislation is felt, and then, said Sir Eric, it could well be too late to save some of the estuaries.

The commission calls on the govern-

ment to use existing legislation and to make full use of voluntary controls to limit the pollution of estuaries. It also calls on the government to bring all effluent discharges to tidal waters and estuaries under control by July 1974 at the latest and to include discharges from ships within the legislation.

One of the tasks of the new regional water authorities should be to monitor sewer discharges, say the commissioners, and the water boards should have statutory powers to take samples from private sewers and to ban the dumping of certain effluents.

Sir Eric said that the commission would like to promote the idea of a

NRDC

Profit and Loss

THE National Research Development Corporation (NRDC) chalked up a profit of £179,000 in the year ended March 1972 in spite of the uncertainty that has surrounded it during the past year or so. The corporation's annual report, published this week, predicts that it will "probably be self-financing for the next few years", but it also records that the number of new development projects started during the year was forty, less than half the number in the previous year (*Twenty-third Annual Report*, HMSO, 1972; £0.47).

The fall in investment on development (from £5.9 million in 1970/71 to £4.3 million in 1971/72) can be explained both by a reluctance on the part of companies already involved in joint ventures with the corporation to maintain their expenditure at previous levels (in real terms) and by a lack of new proposals, says the report, and it goes on to attribute the state of affairs to the onset of "a period of contraction in industrial research and development expenditure which could have an impact in the corporation's outgoings in the future". A total of £8.7 million was earmarked for future development in March 1972, 24 per cent less than a year previously.

In 1971-72, 2,362 inventions were submitted to the corporation, and of these 216 were from government departments, 65 from research councils, and 29 from hospitals. The year before 368 submissions came from these three sectors, with 274 from government departments. Of 312 patent rights assigned to the corporation in 1971-72, 108 originated in government depart-

ments and 43 in the research councils.

A hundred and thirteen new licence agreements were entered into in 1971—twelve with foreign companies—compared with ninety-four in the previous year, and the licence income increased by £0.8 million to £4.5 million. The corporation's best money-spinners continue to be cephalosporin, tri-iodothyronine, and the pyrethrin analogue insecticides. A potato planter invented by a private person is also justifying the interest that the corporation has taken in it.

Among the development projects which the corporation launched in 1971/72 is one involving the Medical Research Council and the Wellcome Foundation in an effort to find modifications of insulin which will both increase the time for which natural insulin is effective and control blood sugar levels to a greater extent. The corporation has also begun to sponsor work at the Fulmer Research Institute — a contract research organization owned by the Institute of Physics—on techniques for coating metals with protective layers of alumina, and it is now involved in a joint venture with Metals Research Ltd with the aim of producing gallium phosphide lamps at a sufficiently low cost for their manufacture to be a commercially viable proposition.

Other new departures include the formation of Vickers Oceanics Ltd, a company partially owned by the corporation and specializing in underwater engineering work, and a joint venture with Com-Rad Electronic Equipment Ltd to develop more accurate devices for the measurement of noise in the context of radar and telecommunications. The corporation is also becoming involved in developing the techniques of fluidized bed combustion.

pollution index as used in their report. This index, which measures the amount of pollution produced per unit of product used, gives a sensitive measure of whether companies are responding to the demand to reduce their output of pollutants.

MINING

Zuckerman Reports

THE Commission on Mining and the Environment has done little to resolve the dilemma of whether mining should be allowed in Britain's national parks. The commission's report, published last week, recommends minor amendments to planning procedures and better ways of controlling pollution and the rehabilitation of land after mining, but passes no final judgement on the issue of mining (*Report of the Commission on Mining and the Environment*, Commission on Mining and the Environment, London, £1.25).

The commission, set up over a year ago by several mining companies and headed by Lord Zuckerman, set about its task following a public outcry when Rio Tinto Zinc Ltd applied for permission to prospect in the Snowdonia National Park. When the commission was set up the company said that it would abide by the findings of the commission. It will not be cast down by the recommendations.

Lord Zuckerman said last week that the commission had not shirked its duty as it had not been asked to decide where, or where not, mining should be carried out. "We accepted the planning laws as they were", said Lord Zuckerman. He went on to say that only the government could decide whether the need for minerals and economic considerations should override environmental considerations.

The commission recommends that the Town and Country Planning General Development Order should be amended to allow mining for non-ferrous metals in all areas—including National Parks—if planning permission is granted. The commission does, however, concede that the local planning authority can, as at present, disallow mining in certain areas.

The commission comes out strongly against applications for exploratory drillings being linked to applications to mine. It argues that granting of permission for an exploratory drilling does not imply that mining would necessarily be permitted at that site.

Information should be provided to local inhabitants about possible mining operations—provided normal commercial security is observed—says the committee. The commissioners also consider what should be done if a mining company fails in its obligation to restore

the land after mining. The reasons for such failings could be many, but the report is particularly concerned with the effects of the mining company being declared insolvent. To avert public mistrust, the commission suggest, that the government invites the mining companies to suggest ways by which problems arising from potential financial difficulties can be avoided. In particular, the commission recommends that a Renewal Trust be set up to which the mining companies should contribute.

The commission also expresses some concern about the effects a mine will have on the local environment. It suggests that as much water as possible should be recirculated within the site and toxic materials produced at the site should be dealt with there. Vehicles using public roads should be regularly washed and mine traffic should not be allowed to lead to road congestion. Noise generated at the site should be minimized by using baffles, buildings and trees, and silencers and baffles should be attached to machinery. The commission also recommends that finely ground materials which could give rise to dust should be handled within buildings.

DISARMAMENT

Pugwash at Oxford

THE twenty-second Pugwash conference ended last week with the future of the organization very much a question mark. The communique issued after the meeting contained the usual pleas for greater speed in disarming, statements on the problems of developing nations and even suggestions on how to deal with pollution and the world population explosion. To cap the lot the conference reiterated its views on the war in Vietnam, first put forward a month ago, which end with a plea to the American people—"How much longer will you tolerate this slaughter?"

Pugwash's involvement with Vietnam followed reports of dykes in North Vietnam being breached by American bombs. Pugwash called on the President of the United States and his air force generals to stop the bombing so that the dykes could be repaired. Last week's statement, however, goes further and it criticizes the policy of the United States in "Vietnamizing" the war. This, the statement says, has resulted in greatly reduced American casualties but "at the expense of enormously increased Vietnamese casualties". Politically, says Pugwash, this is "more expeditious, but to that extent even more condemnable".

The conference suggests that present anti-ballistic missile sites in the United States and the Soviet Union are now at

a level which is "military meaningless and a waste of resources". Consequently, Pugwash suggests that all existing ABM sites be dismantled and a ban placed on all further deployment of the missiles. This, says the conference, should be one of the objectives of the Strategic Arms Limitation Talks.

One of the worries of the conference was that unless a world devoid of nuclear weapons is achieved soon, some non-nuclear weapons countries "may not tolerate remaining indefinitely in a position that is perceived as an inferior one". The barriers between nuclear and non-nuclear states will, as technology advances, become less formidable, according to Pugwash.

The conference felt that the United States and the Soviet Union, which carry out underground nuclear tests for peaceful purposes, cannot justify, in the short term, their claims that such tests will be beneficial. Such test programmes, says Pugwash, are little more than "an excuse for acquiring a nuclear weapons capability".

Pugwash casts its net wide over the pollution and population fields and its comments range from the Stockholm Conference on the Human Environment, whose recommendation for the gathering of data to set international standards are supported, to problems of population growth, for which a multi-disciplinary approach to a solution is recommended. The conference especially endorses a recommendation that a centre for population studies be set up in Sweden, with the chief aim of allowing social scientists to work closely with other scientists on designing plans for new approaches to fertility control.

The conference also called for an integration of the teaching of science and its impact on society. Scientists must also communicate better with other scientists and with society, says Pugwash, so that misunderstandings can be avoided. The scientist should, as well, be aware of his social responsibility and he should defend human rights.

The conference failed to reach agreement on action to be taken when scientists are mistreated in their own countries. Some delegates felt that any action to be taken should be the responsibility of the scientists of that country, whereas other delegates felt that information on such mistreatment should be collected on an international scale.

The conference agreed, however, that no obstacles should be put in the way of scientists who wish to change their citizenship and the delegates "deplored the expulsion of people from their homelands" — these practices, it said, being in violation of the United Nations Declaration of Human Rights.

NEW WORLD

Technology Assessment Comes to Congress

by our Washington Correspondent

THE chances that Congress will get its own Office of Technology Assessment suddenly brightened last week. A proposal to establish the office swept through the House of Representatives in February and also looked set fair to sail through the Senate, but it was eventually bogged down in the Senate Rules Committee and seemed destined to stay there until Congress disperses for the elections. But last week the committee passed the bill and the very next day it breezed through the Senate without debate. All that now remains is for a conference committee to reconcile the differences between the House and the Senate versions of the bill.

The Senate Rules Committee made a few changes to the House version of the bill, chiefly in the composition of the policy-making and executive boards. The purpose of the office will be to give Congress an organization for evaluating the likely consequences of legislation concerned with science and technology—the decisions to abandon the SST and perhaps the water pollution control bill are examples—and it would also have the power to undertake studies on its own initiative. The studies themselves would usually be contracted out, but the bill does allow the office itself to establish special ad hoc task forces. What is still at issue is the extent to which the workings of the office will be subject to the control of a committee of Congress, and in particular, which committee.

The original proposal was fostered by the House Committee on Science and Astronautics, which kicked the idea around for seven years before it was finally brought to the floor of the House of Representatives. The Committee's intention was to put policy and executive authority for the office in the hands of a board consisting of members of the public together with members of Congress, but when the bill came before the House, Mr Jack Brooks, a Democrat from Texas, offered an amendment designed to limit membership of the board to members of Congress—five from the House and five from the Senate, including six from the majority party. The amendment, which caught the bill's sponsors entirely by surprise, was passed and has been a bone of contention ever since.

For one thing, it so happens that Mr Brooks is the chairman of a rather obscure committee called the Joint Committee on Congressional Operations,

which has exactly the composition of his proposed board. His move has therefore been interpreted as an attempt to wrest control of the office away from the Committee on Science and Astronautics. For another, many supporters of the idea of the Office of Technology Assessment have argued that Mr Brooks's amendment may stifle the workings of the body because it would be subject to the everyday pressures of Congress, and in particular to the whims of the majority party.

The Senate Rules Committee has now gone some way towards meeting these criticisms. In the first place, it has made each party equally represented on the board and it has also inserted an advisory committee into the structure of the office's policy-making machinery. The Advisory Committee would consist of twelve members, ten members of the public plus the Comptroller General of the United States and the Director of the Congressional Research Service. It will review and make recommendations to the board on the activities undertaken by the office, and it will also have the authority to review the findings of any assessment made by the office. Clearly, it will put some of the control of the office's activities back in the hands of independent experts, which is where the Committee on Science and Astronautics wanted it in the first place.

The chief initiative for studies undertaken by the office will come from chairmen and minority leaders of committees of Congress (the Senate Rules Committee estimates that about thirty committees deal with legislation concerned with science and technology), but the board will also have the authority to initiate studies. The idea is that the office itself will consist of a director, appointed for a term of six years by the board, and a small staff. It will also use the resources of the Congressional Research Service and the General Accounting Office. As for the methods of technology assessment itself, the bill passed last week explicitly instructs the office to maintain liaison with the National Science Foundation which will award grants and contracts for the development of methods and concepts.

The Senate passed the bill last week just in the nick of time, for if it had been left for another week its chances of getting to the Senate floor before Congress disperses for the election would have been slim. The reason why it has been held up for so long in the

Senate Rules Committee is that Senator B. Everett Jordan, its chief sponsor in the Senate and chairman of the subcommittee of the Senate Rules Committee to which it was referred, has been engaged in a tough primary election in his home state of North Carolina. Senator Jordan eventually lost the election, and his absence from Congress next session would seriously weaken the chances of resurrecting the bill if it is not passed this year.

SATELLITES

Cosmic IMP

by our Washington Correspondent

THE ninth and most complex in NASA's series of Interplanetary Monitoring Platforms, IMP-H, is due to be launched this week. The satellite may be the last in the IMP series, for although a sister satellite is scheduled for a year from now, financial difficulties at NASA may have placed it in jeopardy. IMP-H's mission will be to study the Earth's magnetic tail and to monitor cosmic rays, the solar plasma and magnetic fields near the Earth.

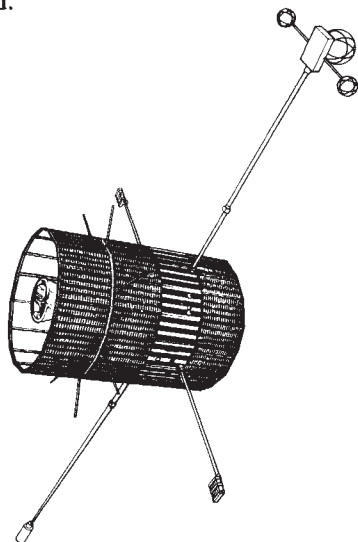
The satellite will be launched into a circular orbit about 450 km in diameter, which will take it through the magnetic tail and also enable it to monitor the interplanetary medium. Its period of orbit will be about 13 days, and one of the chief objectives will be to gain a better understanding of the dynamic processes that take place in the magnetic tail, especially in relation to changes in the solar plasma.

The solar wind impacting on the magnetosphere compresses the magnetic field on the side towards the Sun and draws it out on the dark side of the Earth, but the size of the magnetic tail changes from time to time. In particular, during periods of high solar activity such as the intense solar flares last month, energy from the solar wind which is stored in the magnetotail is suddenly released to create auroral disturbances. IMP-H will be on the lookout for the timing and nature of such events.

The satellite will also monitor galactic and solar cosmic rays, and it will be used as the Earth reference point for the experiments conducted by the Pioneer missions to Jupiter and Saturn and the Mariner missions to Venus and Mercury.

The IMP series, which was started in 1963 with the launch of IMP-A, has been given high priority by the Space

Science Board of the National Academy of Sciences, but it has already suffered from budgetary stringencies at NASA. The series has, for example, been extended for three years longer than originally intended, and it now seems that IMP-J, which is scheduled for launch in a year's time into an orbit 180° out of phase with that of IMP-H, may never feel the draught of the solar wind.



The success of IMP-H, which will be designated Explorer 47 if it is launched successfully, and the fate of IMP J will have a bearing on the prospects for a planned mission which may be conducted jointly by NASA and ESRO. Earlier this year NASA announced that plans have been made to launch a trio of satellites in 1977 or 1988, which will consist of two Earth orbiting spacecraft and one heliocentric spacecraft, to measure the incoming solar plasma and changes in the Earth's magnetic field. Proposals for experiments on the spacecraft were scheduled to be in this week, and a committee to help plan the mission will be set up from those whose experiments are chosen. So far, no decision has been taken on whether the mission will be given the green light, or on which parts will be funded by NASA and by ESRO. Discussions have, however, centred on the possibility that NASA will provide the larger of the Earth orbiting spacecraft and the heliocentric spacecraft, while ESRO will provide the other Earth orbiting spacecraft.

TUMOUR VIRUSES

New Production Centre

A NEW facility for producing tumour viruses was opened last week near the National Institutes of Health. Built at a cost of about \$1,750,000 for Electro-Nucleonics Laboratories Inc., the new Cancer Virus Purification and Research

Laboratory, as it is called, will be chiefly concerned with supplying cancer viruses to customers, particularly researchers in the National Cancer Institute. Viruses will also be available to workers overseas.

There will be a regular supply of such viruses as murine leukaemia (Rauscher and Moloney) and feline sarcoma, but a particular feature of the service which Electro-Nucleonics is planning to offer will be the production of workable quantities of virus from infected tissue cultures supplied by the customer. Most of the isolation and concentration of viruses will be performed by ultracentrifuges developed by the parent company.

The production facility will have negative air pressure rooms, the lowest pressure being in the most hazardous areas, to guard against escape of viruses, and the concentration, morphology and purity of the viruses will be checked throughout production by electron microscopy as well as biochemical and immunological techniques. All of this sounds remarkably similar to what is being offered by the new facilities in Building 41 at the National Institutes of Health and at Fort Detrick, and it throws up the question of why these facilities are being duplicated. Part of the answer lies in the fact that several cancer researchers suggested last week that they are often frustrated by their inability to obtain sufficient quantities of high quality virus material to satisfy their experimental needs. They are hoping that privately owned facilities of this sort may answer some of the problems.

NUCLEAR FUELS

Japan buys American

by our Washington Correspondent

PART of the trade package announced by President Nixon and President Tanaka after their meeting in Hawaii entails an agreement under which the Japanese government will purchase some \$320 million worth of uranium enrichment services from the US Atomic Energy Commission. The idea is that the AEC will supply enriched uranium in return for un-enriched uranium from Japan and a cash adjustment. The agreement itself is not startling since the AEC already has contracts with overseas customers dating from 1969, which together add up to about \$2,000 million, but what is more interesting is a related agreement which was negotiated at the same time.

It seems that the AEC has agreed to study the feasibility of constructing a fourth enrichment plant in the United States, financed jointly by Japanese and US interests. Such a joint venture has

not been conducted before, and at a cost of some \$1,000 million it would be a huge undertaking. So far the AEC has said simply that it would have no objection to studying the feasibility of such a project, and a joint working group will probably be set up soon.

The United States also announced a year ago that it is prepared to enter into negotiations with other countries for the licensing of US enrichment technology, but although such discussions have taken place, an official of the AEC said last week that no firm proposals have yet been put forward. An agreement between the United States and Japan to construct a joint plant on US soil would, however, bypass some of the classification problems that are likely to stand in the way of such licensing agreements.

DES

FDA in Trouble Again

by our Washington Correspondent

WHEN the Food and Drug Administration last month banned the manufacture of the synthetic hormone diethylstilboestrol (DES) for use in animal feeds, it seemed that the agency's headaches over this particular additive were nearly over. But the FDA's knack of getting itself into trouble, no matter what action it takes, has not failed it. The problem now is that the FDA has allowed existing stocks of DES, which promotes growth of sheep and cattle, to be used until the end of the year. The agency has been attacked by a variety of groups and individuals for delaying the ban, Charles C. Edwards, the FDA Commissioner, has been hauled before two Congressional committees to explain his actions and bills have been introduced into Congress to get the hormone off the market. But the hardest blow came last week when the General Accounting Office ruled that the FDA is acting illegally in delaying the ban.

DES is an extremely potent carcinogen which has been found not only to cause cancer in animals, but which has also been linked with several cases of a rare cancer of the vagina in young women whose mothers took the drug during pregnancy to prevent miscarriage. A rigid clause in the food and drug laws, known as the Delaney Amendment, prescribes that an additive which causes cancer when fed to animals must not get into the food supply and the FDA was forced to ban DES treated feeds when it became clear that the hormone could not easily be prevented from turning up in meat. But Dr Edwards allowed DES to be used until the end of the year because "there is no evidence of a public health hazard" and "an immediate ban on the use of

DES in feed could result in an unwarranted public concern and an unjustified increase in meat prices".

Mr L. H. Fountain, chairman of the subcommittee on Intergovernmental Relations, which oversees the work of the FDA, was not satisfied and asked the General Accounting Office for its opinion on the legality of delaying the ban. A letter signed by R. F. Keller, Acting Comptroller General of the United States, which was received by Fountain last week, concluded that Dr Edwards has no legal authority for delaying a ban on a food additive which is found to cause cancer in animals. Under the terms of the food and drug act, Edwards has the power only to withdraw the licence for such an additive, and the practical consequences of such a ban are immaterial to the law. The GAO therefore believes that Dr Edwards has acted illegally in not bringing the ban into effect immediately. So far, the FDA is not offering any comment on the letter, except to say that it is under study.

If the FDA is forced to take DES off the market immediately, and also has no power to grant a stay of execution on other food additives, there is likely to be an increase in the clamour for compensation from the food and drug industry. Already Congress is considering a bill which would provide compensation to food manufacturers caught with large stocks of cyclamates when the FDA took the sweetener off the market in 1969, and a heated debate

is taking place over the merits of such a handout.

The food industry claims that the ban came without warning and caused large losses, while opponents of the bill point out that doubts were raised about cyclamates as early as the 1950s and yet the food industry increased the use of the sweetener from 5 million to 17 million pounds in the 1960s. The argument therefore is that the food industry has only itself to blame for the large stocks of the sweetener that it was caught with when the ban came into effect. The bill to bail the industry out was passed by the House of Representatives earlier this year and it is now being considered by the Senate Judiciary Committee. Pesticide manufacturers are also watching the bill's progress closely because they have also been financially affected by government bans on hazardous chemicals.

NIH

A Quick Trim

by our Washington Correspondent

THE House Appropriations Committee has trimmed some \$935 million off the appropriations bill for the Departments of Labour and Health, Education and Welfare that President Nixon vetoed last month (see *Nature*, **238**, 428; 1972). Among the agencies to which the appropriations committee has been forced to apply the knife is the National Institutes

of Health, whose budget has now been fixed at \$2,497 million, compared with \$2,724 million in the vetoed bill. Of this sum, \$1,705 million is earmarked for the research institutes (as opposed to administration, health manpower, overseas expenditure and buildings), compared with \$1,794 million in the original bill. Nevertheless, even under the revised bill, the research institutes would end up with about \$229 million more than they received last year and \$125 million more than the Administration asked for.

As for individual institutes, \$7.5 million has been trimmed from the vetoed budget for the National Cancer Institute, and \$25.6 million from that for the National Heart and Lung Institute. Both are still set to receive much more than President Nixon requested, however, although the funding falls short of the amounts contained in the much publicized bills calling for a crusade against cancer and cardiovascular diseases which Congress has passed recently.

Although the revised appropriations bill would entail nearly \$1,000 million less expenditure than the vetoed bill, it is still some \$836 million more than President Nixon requested. In view of the fact that President Nixon said in his veto message that he would not be satisfied unless Congress reduces the overall spending to a level very close to his original request, there is a possibility that he may cast a second veto if the Appropriations committee's revised bill survives the rest of the Congressional mill unchanged. The Senate Appropriations committee has not yet reported its revised bill, although it will probably stick fairly closely to the lead given by the House, and there seems little prospect that the bills will be radically altered when they come up for debate. If President Nixon does cast a second veto, however, backers of the new bill are confident that they can muster sufficient votes in the House of Representatives to override it.

CONGRESS

Another Chairman Unseated

by our Washington Correspondent

WAYNE N. Aspinall, the powerful chairman of the House Committee on Interior and Insular Affairs, was defeated in a primary election in Colorado last week, thereby losing the right to seek re-election to the House of Representatives as a Democratic candidate in November. Aspinall, whose chairmanship of the interior committee makes him one of the most influential members of Congress on matters dealing with resource development and the environment, has come under spirited attack by environmentalists in the past few years and this played a large part in his defeat. He has often been criticized, for example, for supporting economic development of resources, particularly the construction of dams, at the expense of the environment—a philosophy no doubt coloured by the fact that for his 24 years in Congress Aspinall

has represented a district containing mining, logging and ranching interests. Earlier this year, a Washington based environmental organization called Environmental Action placed Aspinall on a list of "Dirty Dozen" congressmen who, according to the organization, have particularly poor voting records on environmental issues.

First elected to the House of Representatives in 1948, the 76-year-old Congressman has ruled the Interior committee for 12 years; he is also a long serving member of the Joint Committee on Atomic Energy and chairman of its subcommittee on Raw Materials. Next in line for chairmanship of the interior committee is James A. Haley of Florida, who is only three years younger than Aspinall. The victor in the primary election last week was Dr Alan Merson, a professor of law at the University of Denver.

Short Note

Prostate Cancer

The National Cancer Institute has awarded contracts worth \$622,800 for research into cancer of the prostate. The disease, which is the third most frequent cause of death from cancer among males in the United States, is little understood and there have been suggestions that its study has been relatively neglected. The studies funded by the contracts will be aimed at finding a valid animal model for the disease in man, and also at understanding the metabolism of the prostate under normal and cancerous conditions.

NEWS AND VIEWS

Sea Level and Natural Disasters

At not infrequent intervals the sea rouses itself with sufficient force to bring about catastrophes that make a fair bid to rival mankind's own efforts to undo himself. It is natural that oceanographers and meteorologists in particular should study the processes involved in the expectation that understanding will contribute to the alleviation of a substantial amount of human (and economic) suffering.

One such group of events, known as storm surges, is the subject of two communications by Das and by Flierl and Robinson on pages 211 and 213 of this issue of *Nature*.

These events would seem to an observer at the coastline like unexpected yet inexorable rises in sea level over the course of many hours, and are a consequence of severe atmospheric depressions moving in over the shallow continental borderlands. The effects are often critically dependent on the path and rate of progress of the depression and the topography of the seafloor.

The surface of the sea responds significantly on time scales spanning many orders of magnitude, and over much of this range the responses have a significant effect on man and his environment. The inputs that must be considered are those from the atmosphere, both synoptic and climatological, the gravitational attraction of the Moon and Sun, and geological events, again either climatological or sudden as in the case of earthquakes.

In part the catastrophes are a result of their unpredictability. The tides are, in their time scale and amplitude, of the same order as the storm surges. Yet because tides are a response to the known gravitational attraction of the Sun and Moon, they are essentially predictable and periodic. A "black box" approach of input, transfer function and response has proved to be adequate for many practical tidal problems in the past. At the same time their study allows the important dynamical processes and boundary conditions that contribute to the transfer function to be probed more deeply, and light to be shed on the less predictable events.

Another example of the unpredictable and catastrophic is to be found in the generation of tsunami waves by large seismic disturbances below or close to the seafloor. Once started their propagation is well accounted for in classical hydrodynamic terms, but their direct effect on the coastlines where they dissipate some of their energy is still a matter of intense scientific study and of serious consequence, particularly in the Pacific.

At higher frequencies, in the region of the spectrum dominated by the sea and swell waves, much theoretical and practical progress has been and continues to be made in our understanding. In consequence, the development of good forecasting techniques of value to the navigator and marine engineer is now possible.

At the lower frequencies, characterized by periods of decades to centuries, the water balance of the oceans as a whole and the response of the Earth's crust to the changing distribution of load on it create another class of problems.

The study of the part of the spectrum associated with

storm surges is being approached in current research from several directions. The approach in terms of a semi-empirical transfer function relies for its success on the good documentation of a substantial number of surges both as regards the meteorological input and the resulting surge. Even then good physical insight is needed to select an appropriately simple parameterization of the meteorological data. These data are only available for relatively few of those parts of the world that are subject to surges, although in the North Sea, for example, it was possible to pioneer the method in the 1930s. A second approach, involving statistical methods for the study of the extremes (tails) of probability distributions, is of significance in the long term planning and construction of sea defences. Again, a substantial number of historical data are required. It is of interest that many of the statistics studied so far for extreme surge heights fit rather well with Fisher and Tippett's extreme value distribution, showing a growth without limit albeit with decreasing probability and rapidly widening confidence limits. One physical interpretation of this result is perhaps that surge heights have never yet reached a state in which other physical constraints, such as non-linearities, depth of water and meteorological conditions, are limiting. Theoretical studies, though rarely directly applicable to the real ocean, have established, through simplified modelling, the important effects of the Earth's rotation and the non-linear interactions that can in real situations be significant enough to invalidate a simple linear additive solution of the combined surge and tidal problem. Moreover they provide the formalism necessary for perhaps the most promising attack on the prediction problem—by numerical or analogue solution of the equations of motion.

It is this approach that is adopted by the authors of the two communications in this issue along with many other oceanographers. It remains applicable even if the data from past surges are not substantial; but the meteorological input still needs to be well defined. Both authors remark on the difficulties of assessing the accuracy of the data, and this is reflected to an extent in the details of their conclusions.

Flierl and Robinson have adopted the view that what is most urgently required on the coastline of the Bay of Bengal is some immediate, though limited, oceanographic forecasting techniques to complement the meteorological predictions. In this approach they recognize the fallibility of detailed aspects of their numerical model, while extracting those parts of its results which can be used with some degree of confidence to predict the gross features, such as the maximum height, of the surge. This is expressed as a function of the path of the cyclone, its speed of progress and the wind speed.

In his contribution Das develops one particular model in more detail and tests it against one surge (the most disastrous). This to some extent reflects the considerable interest now being shown at several laboratories in the possibility of developing models of surges that are directly coupled to numerical weather predictions.—From a Correspondent.

"Seeing" Nitrogen Nuclei

WHEN the Apollo astronauts reported observing flashes of light inside their cabins on the way to the Moon, considerable interest was aroused. Were these flashes due to some form of hallucination or did they represent a new and unexpected visual phenomenon? The interaction with the eyes of highly charged, heavy cosmic ray nuclei, which are present in space but are screened from the Earth's surface by the atmosphere, was soon suggested as a possible cause of the flashes, and the article by Budinger, Lyman and Tobias on page 209 of this issue of *Nature* does much to clarify the possible processes involved. Appropriately enough, it was Tobias who, more than a decade before the Apollo flights, made the suggestion that "a dark-adapted person should be able to 'see' very heavily ionizing single tracks as small light flashes".

The early explanations of the effect centred on two chief possibilities, either that relativistic cosmic rays produced visible light by Čerenkov radiation within the eye media, this light then being detected by the retina in the normal way, or that the particles interacted with the retina directly to produce a phosphene or sensation of light, probably by ionization and excitation. Both these mechanisms would be expected to produce a stimulus proportional to the square of the particle charge. Other mechanisms considered included fluorescence in the lens of the eye and direct stimulation of the optic nerve or visual cortex. In view of the known abundance of cosmic rays in space, however, it was generally agreed that to explain flashes of the type and rate observed by the astronauts, relatively highly charged ($Z \geq 6$) cosmic ray nuclei must be responsible. During the studies in technical laboratories that followed, several investigators demonstrated that fast neutrons, muons and helium nuclei could induce flashes in the eyes of observers adapted for the dark, but until recently it was impossible to investigate under controlled laboratory conditions the effect of highly charged nuclei.

In their experiments Budinger and his colleagues have been able to explore the effect of such nuclei by making use of the beam of energetic nitrogen nuclei recently made available at the Berkeley Bevatron. Moreover, they have controlled the direction, position, energy and cross-section of the beam much more precisely than in any earlier study. The results convincingly demonstrate that the nitrogen nuclei can cause flashes and that they can do so by direct interaction rather than by Čerenkov emission. This does not, of course, entirely rule out the possibility that some of the flashes seen by the astronauts were due to Čerenkov effects from relativistic particles. The flashes induced by nitrogen were colourless and, apparently, were brighter than those produced by nuclei of lower charge. Judicious changes in the position of the beam showed that the flashes were most easily seen when the particles stopped in the posterior part of the retina, relatively close to the fovea. No phosphene could be evoked by passing the particles through the visual cortex. Subsidiary experiments indicated that fluorescence in the visible spectrum is unlikely to be involved.

What is still uncertain after these experiments is the nature of the retinal interaction responsible for the

flashes, although the Berkeley workers again suggest that it is in some way related to ionization and excitation; possibly fluorescent ultraviolet photons generated in the immediate vicinity of the particle tracks also play a part. Adaptation to the dark obviously enhances the visibility of the flashes, which suggests that the retinal rod system may be implicated. It is, at first sight, surprising that the phosphenes were only seen when the particles traversed the posterior retina, corresponding apparently to a portion of the visual field roughly 30° in radius. In rod vision, the retinal sensitivity to visible light is relatively low at the centre of the visual field, peaks at about 20° and remains fairly high out to field angles of at least 60° . It may be possible to explain the experimental findings in terms of the beam-eye geometry used, for the particles were travelling roughly tangentially to the retinal surface in the posterior portion of the eye and might therefore be expected to have a longer effective length of track in this region. Possibly, too, the superior pattern recognition abilities of the central retina might bias the observers in favour of reporting more streak and star phenomena in the centre of the visual field. Interesting questions concerning the psychology of the perceptive process are also raised by the reported impression of motion in the flashes. Undoubtedly, more detailed study of these effects, taking full account of the detailed properties of the retina, will do much to clarify the character of the interaction and the precise retinal level at which it occurs. Studies of the electroretinogram induced by particles would obviously be helpful in this respect.

The other aspect of this work which must interest future space voyagers is the problem of the possible health hazard that such charged particles represent both to the eye and to other portions of the body. Although at present it has not been demonstrated that the flashes correspond to the occurrence of any retinal damage, other Berkeley studies have shown that degeneration occurs in the retina of a mud-puppy (*Necturus maculosus*) exposed to the nitrogen beam. Comstock and his colleagues at the General Electric Research Centre have already estimated from studies of particle tracks in helmets used in the Apollo missions that substantial loss of visual cells could be caused by cosmic rays during prolonged space missions with present standards of spacecraft shielding (*Science*, **172**, 154; 1971).—W. N. C.

Caecilian Fossil Found

THE least known of the three orders of living Amphibia, frogs, toads, newts and their allies, are the wormlike caecilians. These are completely limbless, burrowing forms with reduced eyes and virtually no tail. Most features of their anatomy are obviously related to their mode of life, but some genera retain minute scales, buried beneath the surface of the skin, which are certainly an inheritance from Palaeozoic amphibian ancestors. Scales are unknown in the other two extant amphibian orders, the Anura, or frogs and toads, and the Urodela, or newts and salamanders.

Numbers of fossil forms pertaining to both the Anura

and Urodela are known, mostly from the Cainozoic era, but until the account by Estes and Wake (see page 228 of this issue of *Nature*) no authentic caecilian fossil was known. The single, but quite diagnostic, vertebra described in their communication is the first stage in the filling of an important gap in the fossil record. The specimen comes from the Palaeocene of Brazil. The time, at the beginning of the Cainozoic, is surprisingly early and the locality, as the authors point out, may be at odds with the present distribution of genera within the order.

Estes and Wake conclude that their fossil vertebra resembles those of an extant African genus more than it does the vertebrae of any New World form. This leads them to some rather bold speculations on the former distribution of caecilians. Their single vertebra is, however, separated by a time gap of some sixty million years from all other known members of the group, so that even the most tentative conclusions about its relationships within the caecilians seem premature.

The discovery of more skeletal material of this or any other fossil caecilian is eagerly awaited. Should the authors' speculations prove correct it would be demonstrated that essentially modern caecilians had evolved and radiated before the dawn of the Cainozoic Era. This would place the time of origin of the group well back into the Mesozoic, paralleling what is known of the evolutionary history of the other two extant amphibian orders.

The earliest known fossil urodele comes from the Upper Jurassic of the United States, and the earliest fully evolved frog from the Lower Jurassic of Argentina. Before that time the evolutionary history of all three groups is obscure. It is generally but not universally agreed that a small fossil amphibian *Triadobatrachus* (long known as "*Protobatrachus*") from the early Triassic is related to frog ancestry. Earlier specimens, isolated vertebrae from the American Permian and tracks looking like the footprints of a frog from the Permian of South Africa, have been tentatively cited as remains of Lissamphibia (the three living orders) but this has not been generally accepted.

The origin of the Lissamphibia has thus been for many years a rich field for inadequately supported theory and sometimes acrimonious argument. Until relatively recently it was frequently the practice to trace the anurans and the urodeles respectively back to different Palaeozoic ancestral groups. The caecilians were usually ignored or brigaded with the urodeles by default. This separation is retained by Jarvik, who traces the two major groups back to two principal divisions of the Devonian rhinidistion fishes. This

work, although anatomically meticulous, is not generally accepted outside Sweden, for no intermediate forms are proffered to bridge the gap of 400 million years between the Devonian and the present.

Within the past decade the chances of producing a valid hypothesis of the origin of the Lissamphibia have improved. The term Lissamphibia was revived by Parsons and Williams in 1962 to distinguish the extant orders from the totally extinct fossil orders, which had disappeared by the end of the Triassic. It was pointed out that the extant groups were united by a number of specializations, notably cutaneous respiration, and particularly by the key character of pedicellate teeth, in which the crown and root are separated by a region of connective tissue. This type of tooth is otherwise unknown in tetrapods or any related fish group.

More recently Bolt has described a small lower Permian labyrinthodont amphibian with pedicellate teeth and other characters, particularly the structure of the vertebrae, suggestive of Lissamphibian ancestry. It is to be hoped that the caecilian vertebra described in *Nature* this week will be the first of many discoveries of fossil members of that order, so that concepts of Lissamphibian ancestry will take due account of the third and least known group of living Amphibia.—From our Vertebrate Palaeontology Correspondent.

SOLID STATE

Problems with Caesium

from a Correspondent

THE present theoretical framework for the description of the electronic structure of simple metals seems inadequate to describe a new feature in the high

frequency absorption of the alkali metal caesium. This is the conclusion of a careful analysis by J. Hermanson of Montana State University (*Phys. Rev. B*, 6, 400; 1972).

From some points of view the alkali metals should be the simplest metallic systems, and most of their electronic properties are described very well by an independent free electron model in which the effects of the ionic lattice are extremely weak. The predictability of single-particle effects in these materials has made them a favourite hunting ground for the elusive many-electron effects caused by the strong Coulomb interaction that occurs between electrons.

Various theoreticians have suggested that such effects may occur in the optical absorption of metals for photon energies greater than the plasmon energy, and the simplicity of the alkali metals gives the prospect of disentangling many-electron effects from the single-particle effects that produce the optical absorption at frequencies less than the plasma frequency. These are, first, Drude absorption, which is an intraband process involving the emission or absorption of a phonon, and, second, interband absorption. The former dominates at low photon energies ($\ll 1$ eV) and then falls off rapidly, while in caesium the interband absorption has a threshold just below 1 eV. Previous theoretical work had suggested that excitation of collective modes makes an important contribution at frequencies greater than the plasma frequency, and the recent experimental data of Whang *et al.* (*Phys. Rev. Lett.*, 25, 646; 1971) show a prominent high frequency absorption peak at about 5 eV which does not seem to lend itself to interpretation as an interband transition. This was originally interpreted in terms of a collective effect with a threshold at $\hbar\omega_p + \hbar\omega_0$, where ω_p is the plasma frequency and

Transfer of Phage Receptor Sites

A METHOD for transferring the lipopolysaccharide receptor sites for coliphage U3 from phage-sensitive cells to spheroplasts of phage-resistant cells is reported in *Nature New Biology* next week (September 27) by Watson and Paigen. Coliphage U3 adsorbs only to *Escherichia coli* K12 cells that have incorporated galactose into lipopolysaccharides of their cell walls and as a result strains of *E. coli* K12 carrying a *gal* deletion, for example, the strain SA242, resist infection by this phage. When, however, spheroplasts of SA242 cells are exposed to cell wall lipopolysaccharide extracted by phenol from sensitive K12 cells about 1 per cent of the recipient spheroplasts can subsequently be infected by U3 phage par-

ticles in the presence of DNAase, which eliminates infection by naked U3 DNA.

This attachment of the lipopolysaccharides including U3 receptors to spheroplasts takes place in the presence of sodium cyanide, so it does not require energy or *de novo* synthesis of cell wall materials by the recipients. Moreover the acquired receptor sites have a comparatively short half-life, for after about 60 min metabolizing recipient spheroplasts begin to lose their sensitivity to U3. As Watson and Paigen point out it should be possible to transfer receptor sites for other phages in a similar way, and this approach may open new avenues to the investigators of the function and biosynthesis of bacterial cell walls.

ω_0 is the threshold for interband absorption, with a final state consisting of a plasmon and an electron-hole pair. This fits the position of the peak, but Hermanson's calculation of the strength of this plasmon side-band effect concludes that its intensity should be about an order of magnitude less than that observed in caesium. Other explanations for this effect must therefore be sought.

It is worth noting that the study of optical properties of alkali metals is fraught with experimental difficulties associated with the difficulties of producing and maintaining clean flat surfaces on these extremely reactive metals. It has in the past proved very difficult for different laboratories using slightly different techniques to obtain concordant results, and here too it would be valuable to have the results confirmed by a different technique.

CYCLIC AMP

Omnipotent Nucleotide

from our Cell Biology Correspondent

THESE days cell biologists seem to be attracted to neuroblastoma cells almost as inevitably as iron filings are drawn to a magnet, for neuroblastoma cells can be maintained in culture, they can be induced to differentiate into nerve-like cells with compounds such as dibutyl cyclic AMP (Bu_2 -cAMP) and they are, moreover, malignant. In short, cultivated neuroblastoma cells provide an *in vitro* experimental system with which such fashionable problems as the molecular basis of differentiation and malignancy and the role of cyclic AMP in the regulation of cell division can be explored; and the ripe and the not so ripe fruits of such labours are appearing with regularity in the literature. Waymire, Weiner and Prasad, for example, have recently reported (*Proc. US Nat. Acad. Sci.*, **69**, 2241; 1972) measurements of the changes in the activity of tyrosine hydroxylase in cultures of neuroblastoma cells after exposure to Bu_2 -cAMP, to other substituted cAMPs, to papaverine, an inhibitor of cyclic nucleotide diesterase, and to sodium butyrate. Tyrosine hydroxylase is believed to catalyse the rate-limiting step in the synthesis of catecholamines in neuroblastoma cells, and it is therefore a biochemical marker of a differentiated function of these cells.

Waymire *et al.* find that when neuroblastoma cells are explanted and placed in primary cultures the tyrosine hydroxylase activity progressively decreases as the culture ages so that after 7 days the activity is only 2 per cent that of freshly explanted cells. When, however, Bu_2 -cAMP is added at concen-

trations which Hsie and Prasad have shown induce the formation of axon-like processes, not only do the cells undergo this morphological differentiation but also the activity of tyrosine

hydroxylase increases dramatically. But addition of sodium butyrate, a potential breakdown product of Bu_2 -cAMP, also causes a considerable increase in the tyrosine hydroxylase ac-

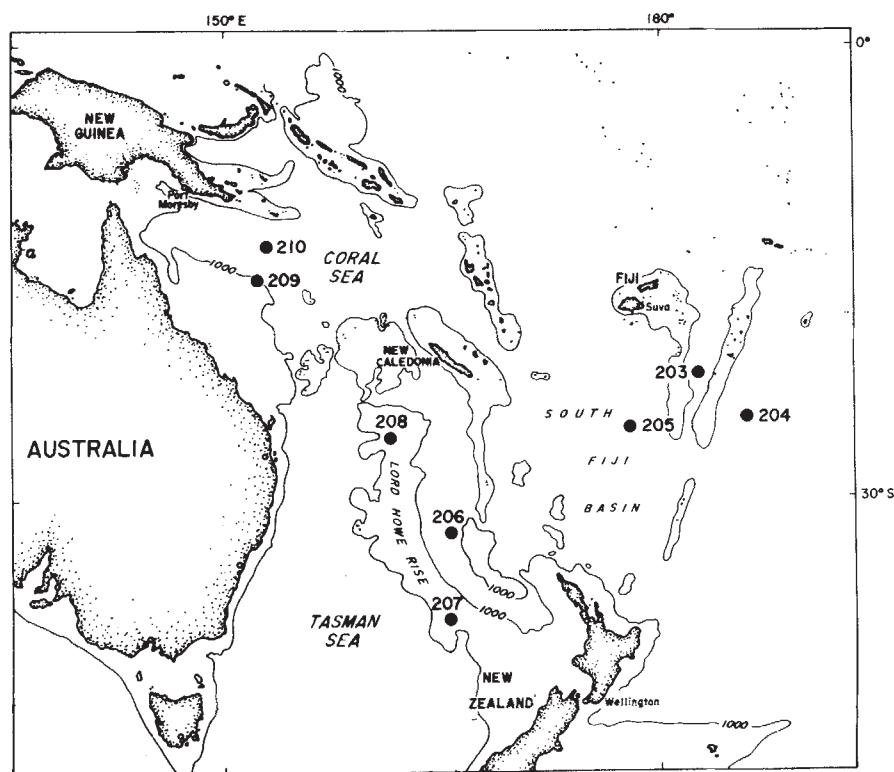
Palaeocirculation in Antarctic Waters

ONE of the less familiar consequences of continental drift and seafloor spreading is the change in oceanic circulation patterns brought about by the contraction and expansion of oceans. The Antarctic circumpolar current, for example, is the largest volume flow in the world and, as its name implies, now runs between Antarctica and Australia along part of its route. Clearly, however, this could not have been the case before the separation of the two continents, which began during the early Eocene and must have produced drastic changes in circulation that could well have influenced the erosion of the deep ocean floor.

In next Monday's *Nature Physical Science* (September 25) Kennett *et al.* report evidence of such erosion during the early Oligocene, based on an analysis of cores obtained from the Tasman and Coral Seas during Leg 21 of the Deep Sea Drilling Project (see map). The essential discovery involved is that of a regional unconformity which is present in both ridge and basin areas at present water depths of 1,400 to 4,600 m. In principle, such an unconformity could have been caused by slumping, but this is usually relatively local unless induced by tectonism; and

most of the tectonism in the area is known to have occurred before the late Eocene. Kennett and his colleagues thus conclude that the unconformity must be explained in terms of erosion effects by particularly vigorous bottom waters.

There is now plenty of evidence to suggest that ancient oceanic circulation patterns are greatly influenced by the glacial history of Antarctica, with intensified circulation occurring during glacial episodes. One of the principal Cainozoic glacial episodes is known to have occurred during the period from late Eocene to early Oligocene; and so it is likely that the chief cause of the erosional unconformity is glacial. At the same time, however, the location of the erosion—and in this case its wide extent—is almost certainly influenced by plate tectonic configurations and their changes. Bearing this in mind, Kennett *et al.* then go on to describe three possible detailed hypotheses which can explain the widespread unconformity in terms of the glacial and tectonic behaviour in the area and which are consistent with observation. At present, the most valid of the three circulation-erosion histories cannot be distinguished from the others.



tivity and a reduction in the growth rate; it does not, however, induce concomitant morphological differentiation.

Waymire *et al.*, who were, of course, out to establish that cAMP, not butyrate, has a role in the regulation of the activity of tyrosine hydroxylase activity in these cells, must have been abashed by this surprising observation. They seem, however, to have convinced themselves that the level of tyrosine hydroxylase activity rises in parallel with increasing intracellular concentrations of cAMP by showing that other substituted cAMPs as well as papaverine induce significant increases in the activity of this enzyme and in some cases concomitant morphological differentiation. They also obtained data which suggest that the increased activity of this enzyme results from synthesis of new enzyme molecules. But the awkward fact that sodium butyrate induces an increase in the activity of tyrosine hydroxylase remains. Not everyone will be satisfied with the suggestion that sodium butyrate may be mimicking the action of neurobiologically active molecules such as γ amino and γ hydroxy butyric acids but no doubt cells in more than one laboratory are about to taste sodium butyrate.

Prasad and Sheppard (*Exp. Cell Res.*, **73**, 437; 1972) have also recently reported that papaverine and two other inhibitors of phosphodiesterases induce the formation of axon-like processes by neuroblastoma cells. This response to these inhibitors, which for the first 24 h is reversible but thereafter is irreversible, apparently precedes the maximal inhibition of cell division. Prasad and Sheppard conclude, therefore, that the morphological differentiation is probably a direct response to the inhibitors of phosphodiesterases rather than a secondary response to the inhibition of cell division. But they were obviously in a justifiably cautious mood when they wrote this report, for after drawing attention to the fact that these inhibitors might be expected to cause an increase in the intracellular concentration of cAMP and having noted that Bu_2 -cAMP and prostaglandins also induce the formation of axonal processes, they caution that "these data, as yet, are inadequate to suggest any direct role of cyclic AMP in the differentiation of neuroblastoma cells".

Willingham, Johnson and Pastan (*Biochem. Biophys. Res. Commun.*, **48**, 743; 1972), by contrast, have not demurred at offering a hostage to fortune. They have been investigating the effects of adding Bu_2 -cAMP to synchronized cultures of Swiss 3T3 and BALB/C 3T3 mouse fibroblasts. Bu_2 -cAMP blocked mitosis when added after the cells had entered S phase even though the round of DNA replication was completed; it also blocked entry

into S phase when fed to the cells continuously after replating. In short, Bu_2 -cAMP can block cells in the G1 or G2 phases. No one will quarrel with those conclusions, but Willingham *et al.* further claim that late in G1 phase high concentrations of cyclic AMP hasten the onset of DNA synthesis. Their data, however, show that while Swiss 3T3 cells exhibit this response BALB/C 3T3 cells do not, which means, to say the least of it, that this putative positive regulatory function of cAMP is not universal even to cultivated mouse fibroblasts.

SOLID STATE

Shocked Ceramics

AN interesting correlation between radiation damage and the effects of explosive shock waves is drawn by R. L. Nelson, of the United Kingdom Atomic Energy Authority, Harwell, and D. B. Hartley, of the Explosives Research and Development Establishment, Waltham Abbey, in the latest issue of the *Journal of the Chemical Society, Dalton Transactions* (1596; 1972). Nelson and Hartley compared the reactions of several crystalline ceramics to explosive shocking and high energy radiation by means of electron spin resonance and diffuse reflectance measurements, and they also considered

surface area changes and such physical properties as colour changes.

The importance of a completely ordered structure in crystalline materials has been appreciated for many years, and the properties of metals, for example, are known to be correlated with the density of atomic defects or dislocations. Recently, however, the creation of small scale defects and much larger disturbances of the crystal lattice have assumed some practical importance, in particular in studies of the properties of reactor cores.

Of the three ceramics studied by Nelson and Hartley—magnesia, zinc oxide and silica—only the magnesium oxide showed similar behaviour when it was irradiated with high energy electrons or neutrons and when it was subjected to a shock wave. The silica displayed no correlation between the two processes, whereas only moderate similarities in behaviour emerged from a study of the zinc oxide.

It is significant that in this series of experiments the material with the lowest melting point showed least similarity between damage induced by shock waves and by radiation. It has been suggested by Symons (*J. Chem. Soc., A*, 1648; 1971) that no correlations exist between defects formed in solid materials by explosive shock waves and those formed by radiation, but the

A Precursor of Immunoglobulin Light Chain

ALTHOUGH it is becoming apparent that many, if not all, mammalian proteins are initiated with methionine, studies of amino-acid sequence on the N-terminal ends of immunoglobulins have failed to detect this initial methionine residue. With the report of Milstein, Brownlee, Harrison and Mathews in *Nature New Biology* next Wednesday (September 27) much of the speculation concerning the possible post-synthetic cleavage of the individual heavy and light chains of immunoglobulins will be ended.

By using purified mRNA, polyribosomes or microsomes from myeloma MOPC 21 as the source of mRNA, they have shown that in a reticulocyte cell-free system, the light chain product obtained from mRNA or polyribosomes has a molecular weight about 1,500 daltons greater than the light chain obtained from a microsomal-primed preparation, or from the *in vivo* light chain. Although tryptic digests of the larger molecule (designated P) have established that it contains some peptides identical to light chain synthesized *in vivo*, differences in the N-terminal peptide are seen, establishing the location of at least part of the excess material, presumably amino-acids, at the N-terminal end. Sequence studies

of this new N-terminal sequence will be anxiously awaited.

One of the more striking features of the system is the requirement that membrane should be present at the time of synthesis of P in order to effect the ultimate cleavage to light chain. It should be noted that the specificity of cleavage appears not to be confined to membranes from myeloma cells as membranous material from Krebs ascites cells seems to work equally well.

Although the function of the extra amino-acids is not clearly understood, the hypothesis most attractive to Milstein and his colleagues is that, following initiation of protein synthesis on free ribosomes, the peptide is used to determine which ribosomes become membrane-bound. Alternatively the modified N-terminus may function to initiate an exit through the membrane for the protein being synthesized.

Whether or not the N-terminal sequence is peculiar to immunoglobulin light chains or whether it indeed functions in a more general manner for all secreted proteins will have to await the demonstration and characterization of similar peptides from both additional immunoglobulin chains as well as other proteins.

present results of Nelson and Hartley show that this is not uniformly true and that the higher the melting point of the ceramic the greater the likelihood of a correlation.

Qualitatively the two processes of producing voids have much in common. The advancing front of a shock wave and the path of a high energy particle represent regions of intense disturbance, where defects can be generated and future local super-heating will allow defect mobility to form larger scale aggregations of defects. It seems from these results that the tendency of the ceramic to anneal after shocking is important; the poor correlation between radiation and explosive shocking for SiO₂ may be due to a self-healing process induced by local super-heating during transmission of a shock wave.

ENZYMES

Taking the Strain

from our Molecular Biology Correspondent

ONE of the less equivocal mechanisms that have been advanced by way of a partial explanation of the rate increase in enzymatic catalysis is an increased binding constant for the substrate when it is in its transition state. The best-founded example occurs in lysozyme: Phillips and his colleagues have inferred from their examination of the active centre that when the cleavage site is occupied by an N-acetylglucosamine residue, the hydroxymethyl group in the sugar ring cannot be accommodated unless the stable chair-type pucker gives place to the half-chair, with four of the six ring atoms, including the oxygen, in a plane. This is also the configuration expected in the transition state of the glycosyl transfer reaction, in which one of the ring carbons looks like a carbonium ion. Secemski, Lehrer and Lienhard (*J. Biol. Chem.*, **247**, 4740; 1972) have taken advantage of a recent crystallographic finding—that the δ -lactone derived from the sugar has the half-chair configuration—to test the hypothesis, for if this derivative is indeed sterically equivalent to the transition state of the substrate, the binding constant on the enzyme should be substantially increased over that of the chair-form precursor.

Secemski *et al.* have used a tetrasaccharide in order to satisfy the binding subsites on the enzyme, the terminal sugar unit, which in favourable circumstances enters the cleavage site (D-site), being modified. The δ -lactone is in equilibrium with the free acid, and all binding experiments had therefore to be performed with a mixture of the two, or with the acid alone as a control. Binding measurements were based on the large change in protein

fluorescence, engendered by the proximity of the saccharide residue to the two adjacent active-centre tryptophan side chains. A good comparison of the affinities of the enzyme for its ligands is also afforded by their ability to inhibit competitively the lysis of micrococcal cell walls. Oxidation of the terminal saccharide to the acid results in a large diminution of competitive activity. The mixture of the acid and δ -lactone, on the other hand, exhibits greatly enhanced inhibition, compared with the unmodified tetrasaccharide. Fluorescence titrations of lysozyme

with the latter, with the acid, and with a mixture containing a known proportion of the lactone yield binding constants for the three species. The concentration of lactone required for 50% inhibition of bacterial lysis is two orders of magnitude lower than that of tetrasaccharide, and the measured binding constant at pH 5 is thirty times larger. This is qualitatively in accord with expectation.

The dependence of the binding constants and the fluorescent intensity on pH gives some further information, correction being again made for the

DNA and Daunorubicin in Cancer Chemotherapy

CANCER chemotherapy suffers from the serious drawback that all agents which are effective in killing cancer cells also have detrimental effects on normal cells—cytotoxic drugs and anti-metabolites cause bone marrow depression and ulceration of the gastrointestinal tract by damaging the rapidly proliferating cells at these sites. Methods of obtaining a selective action against cancer cells are obviously of paramount importance, but unfortunately cancer cells have not yet been found to possess any properties that are specifically related to neoplasia. Recent experiments suggest that selectivity may be increased by combining an active chemotherapeutic or radio-active agent with a protein or DNA.

There is good evidence that in several experimental animal tumours the neoplastic cells possess tumour specific antigens. In man, immunological reactions have been found to occur against tumour cells, but the specificity of the reaction is still in doubt. Antibodies have been demonstrated in the serum of patients which react against their own tumour cells, but not against normal cells of the organ concerned. This discovery suggested the use of antibody as a carrier of a radioactive or chemotherapeutic warhead, enabling the active agent to be taken selectively to the tumour. Although ¹³¹I-labelled anti-melanoma antibody has been used in the treatment of patients with malignant melanoma, evidence of a therapeutic effect was very doubtful (*Cancer*, **10**, 999; 1957). Day *et al.* (*J. Nat. Cancer Inst.*, **20**, 1123; 1957) observed ¹²⁵I localized in a cerebral glioma following an infusion of rabbit anti-glioma antibodies labelled with ¹²⁵I.

More recently Ghose *et al.* (*Brit. Med. J.*, **3**, 495; 1972) found that antibody to the mouse EL4 lymphoma and human malignant melanoma could be bound to chlorambucil without causing a loss of alkylating activity or interfering with the reactivity of the antibodies with their respective tumour cells. When given to mice pre-innucleated with tumour cells, the antibody bound

to chlorambucil was a much more effective tumour inhibitor than chlorambucil or the antibody alone. In one patient, injection of melanoma antibody bound to chlorambucil, first locally into a few metastatic nodules and then by the intravenous route, was followed by the regression of all the metastatic nodules.

The communication by de Dève and his colleagues in next week's *Nature New Biology* (September 27) suggests the use of a new drug complex. They combine daunorubicin with DNA to produce a compound that will not diffuse across a cell membrane and requires pinocytosis for uptake into the cell. The complex is then taken into the lysosomes where digestion of the carrier DNA causes the daunorubicin to become biologically active. The capacity of the complex to kill a particular cell will therefore depend upon the pinocytic, lysosomal and mitotic activity of the target cell. A high pinocytic and lysosomal activity is characteristic of many tumour cells, and this may well form the basis for some degree of selectivity. It could be that the mechanism of action of the antibody complexes is similar. The chlorambucil-melanoma antibody complex could be taken up preferentially by the melanoma cells, and selective action need not depend upon specific antibody activity.

Daunorubicin is one of the most effective drugs used in the treatment of acute leukaemia, but bone marrow toxicity and cardiotoxicity can be troublesome. The DNA-daunorubicin complex has a higher therapeutic index than free daunorubicin, which is more toxic. At higher doses better results were obtained with the complex tested against L1210 leukaemia in DBA/2 mice, chiefly because of its lower toxicity. The experiments suggest that the complex may be worth trying in human acute leukaemia. Hopefully, the combination of a therapeutic warhead with an appropriate carrier will provide a series of useful complexes for cancer therapy.

contribution of the acid in the acid-lactone mixture. The upshot is that whereas oligosaccharide binding falls off when the pH rises above about 5, according to a profile identified with the titration of an active-centre carboxyl group (presumably glu-35), of pK about 6.3, the binding constant of the lactone increases through the same region to a plateau extending from about pH 6.5 upwards. It is inferred that, by contrast with the unmodified saccharide, the lactone binds preferentially to the form of the enzyme in which the anomalous carboxyl group is protonated. The consequent suppression of protonation of the group is reflected in the pH profile of the fluorescence when the lysozyme is saturated with the lactone: this now follows a pK curve centred at pH 4.7. These data, however, fail to account quantitatively for the dependence of the binding constant on pH, and it seems that other ionizing groups, most probably carboxyls at other subsites, are also involved. The active centre glu-35, it may be noted, should ionize, when participating in the transition state, because of proton transfer to the attacking group reacting with the glycosidic carbon.

A comparison of the binding constants at the cleavage site is possible only by indirect means, for oligomers of N-acetylglucosamine tend to bind only at the first three subsites, in virtue of the steric obstruction at site D. N-Acetylmuramic acid, one of the constituents of the cell wall, is, however, incompatible with one of the subsites, and when it is present in the appropriate position in the oligomer, a terminal N-acetylglucosamine is forced into the D-site. Binding data so obtained indicate that as between the chair-form sugar ring, and the transition state, for which the lactone may now be regarded as an analogue, there is a difference in association constant approaching four orders of magnitude. This is a measure of the contribution of the transition state structural distortion to the enhancement of the catalytic rate.

Starting from the same premises, van Eikeren and Chipman (*J. Amer. Chem. Soc.*, **94**, 4788; 1972) have employed a different strategy to arrive at the same conclusion. As the steric crowding implicates the terminal sugar ring hydroxymethyl, the elimination of this group should lead to facilitated binding. By saccharide chemists' prestidigitation, van Eikeren and Chipman have converted the terminal N-acetylglucosamine of various oligomers into N-acetylxylosamine, which differs from it only in the absence of the hydroxymethyl group, while at the same time introducing a tritium label for ease of estimation in equilibrium dialysis experiments. This method, as well as

fluorescence titration, was used for the measurement of binding constants. Again, when the presence of N-acetylmuramic acid forces the terminal reducing sugar residue into site D, the binding constant is decreased more than a hundred-fold, whereas N-acetylxylosamine in the same position brings about a fifty-fold increase. The difference between a favourable and an unfavourable interaction at this site (the latter necessitating isomerization of the chair-form) amounts to 5 kcalorie mol^{-1} , which is in excellent accord with enlightened guesses at the corresponding strain energy.

PINNIPEDIA

Seals at Guelph

from a Correspondent

WITH interest in marine mammals riding high as discussion ranges from the conservation of commercially threatened stocks of whales and seals to the underwater sensory perception of these animals it was inevitable that a full scale international symposium on seals would be organized. What is perhaps at first surprising is that the Symposium on the Biology of the Seal, sponsored by the International Council for the Exploration of the Sea (ICES), the International Commission for the Northwest Atlantic Fisheries (ICNAF) and the International Biological Programme (IBP) (with support from several other organizations) should have been held at, and sponsored by, the University of Guelph in inland Ontario. Guelph's interest in seals emanates from its Dean of Biological Science, Professor Keith Ronald, the convener of the symposium, who has established a laboratory stock of harp seals on the Guelph campus. The symposium lasted from August 13 to 17 and was attended by 120 delegates.

The opening address was given by Dr Victor B. Scheffer, a veteran fur seal biologist and author of the standard text on the pinnipedia. Dr Scheffer reminded the assembly that, as members of the scientific community, they need to be aware of new ideas in molecular evolution, energy-systems ecology, the

bioengineering of remote sensing, and many other fields of enquiry. On the other hand, as human beings they have to be aware of changing public opinion.

With a world catch of fish of 69 million t a year, the limit of fish resources is being approached and it might be argued that the deliberate reduction of seals, as important fish predators, would benefit fisheries. This, Dr Scheffer claimed, is an oversimplification of a very complex situation. System models need inputs from common sense and human values. Will it really be necessary to exploit the hitherto untouched stocks of seals in the Antarctic pack ice?

Not all the delegates at the symposium were as sympathetic to these views as Dr Scheffer, however; many of those present clearly thought that rational exploitation of a natural resource was as good a means of conservation as any, though most would admit that a great deal more research was required before the exploitation of many populations could be claimed to be rational. But the fact that, in 1825, James Weddell was able to hold up the harvesting of fur seals at Isla de Lobos, off La Plata, as an example of good management, and that Professor R. Vaz-Ferreira (Uruguay) was able to say that this sealing industry is still in progress, proves that empirical methods can, on occasion, prove effective.

The paper by Dr G. V. Morejohn (Moss Landing Marine Laboratory), classifying the fur seals and sea lions on the basis of the structure of what many biologists have regarded as a relatively undifferentiated structure, the penis bone, attracted considerable interest. The degree of sophistication of the study of seals in captivity was exemplified by the contribution from Dr V. S. deKleer (Ontario Veterinary College) on the electrocardiograph of the harp seal. In this animal the J component of the ECG is almost always clear of the base line, a condition which is regarded as evidence of cardiac disease in man, although apparently normal in the seal. Dr Michael Bigg (Fisheries Research Board of Canada)

Time Delays in Melting Bismuth

A STRANGE aspect of the superheating of bismuth is described in *Nature Physical Science* next Monday (September 25) by Blackman, Peppiatt and Sambles; it seems that particles of bismuth on a carbon film held at a temperature a few degrees above the bulk melting point display a well defined delay in the melting process—the number of particles remaining solid decreases exponentially with time.

Blackman and his colleagues deposited the bismuth in the heating stage of an

electron microscope, and, after annealing, the layer contained thin platelets, each a few tens of nm across. The half-life for the melting of these was about 60 min at the bulk melting point of bismuth, but only about 10 min when the temperature was 5 K higher. After solidification and annealing, however, the bismuth was in the form of polyhedra. It turned out that melting polyhedra showed a similar exponential effect to the platelets, but at a temperature about 5 K lower.

reported that photoperiod was responsible for timing the oestrus cycle in harbour seals from the Pacific coast. Although the response was not observed in all individuals, Dr Bigg suggested that population differences in the timing of oestrus might be due to population-specific responses to photoperiod.

The behaviour section, chaired by Dr R. J. Schusterman (California State College), reflected the strong interest in the behaviour of seals that has been developed at the University of California. It is encouraging now to see comparisons being made in such species as the northern sea lion and the South Australian fur seal. Dr R. L. Gentry (University of California, Santa Cruz) emphasized the value of quantified comparative studies, rather than the descriptive accounts which have predominated up to now. Dr B. J. LeBoeuf (University of California, Santa Cruz) reported the existence of different "dialects" in the threat calls of male northern elephant seals from the colonies off the coast of California.

A section on care and management of pinnipeds indicated the increasing use of seals as laboratory animals. Dr J. R. Geraci (University of Guelph) pointed out the necessity of ensuring that not only the apparatus and chemicals, but also the experimental animals used in physiological investigations, were in first class condition.

A paper by Mr W. N. Bonner (Seals Research Division, Natural Environment Research Council, Lowestoft) illustrated the effect that an increase of seal numbers could have on their environment. At the Farne Islands, grey seals, which have doubled their numbers in the past ten years, are causing destruction of the vegetation and erosion of the soil cap on the islands they inhabit, and are also showing changes in behaviour.

Mr A. V. Holden (Department of Agriculture and Fisheries for Scotland, Pitlochry) referred to the importance of seals as indicators of pollution levels in the surrounding areas, a point already raised by Dr Scheffer. High concentrations of certain environmental contaminants, particularly the organochlorine pesticides and PCBs, have been found in seals. The amounts appear in some instances to be sufficient to have adverse effects on the animals.

PLATE TECTONICS

Energy Balance

from our Geomagnetism Correspondent

ALTHOUGH many different driving mechanisms for plate tectonics have been proposed over the years, none has yet emerged as the clear winner. The latest contribution to the debate comes from Lliboutry (*J. Geophys. Res.*, **77**,

3759; 1972) who looks at the energy requirements for plate motion and, as a result, adds his voice to the growing consensus against the idea of shallow convection cells.

When convection in the mantle was first proposed as the driving mechanism for large scale horizontal movements of the Earth's crust (at that time, continental drift)—thus breaking the impasse which had prevented the acceptance of Wegener's ideas for several decades—it was regarded as a mantle-wide phenomenon. But when the asthenosphere subsequently became more clearly defined, it appeared more appropriate to limit convection to this plastic or semi-fluid layer, or even to get away from convection cells in the true sense and regard the asthenosphere as a return flow channel balancing the motion of the lithosphere in the opposite direction. Today, however, there are hints of a return to, if not mantle-wide flow, at least motion deeper than the asthenosphere.

As a first step towards reinforcing the latter view, Lliboutry considers the energy balance involved in plate tectonics, while admitting that only plausible, rather than exact, numerical calculations are possible. On one side of the equation, the rate of release of seismic energy is taken as 2×10^{10} W, to which must be added an energy rate of the same order of magnitude representing folding and shearing in orogenic areas not associated with earthquakes. On the negative side, too, is the gravitational energy stored by epeirogenic movements. A simple calculation shows that the energy rate involved in the rising of the continents to about 5 km (in 10^9 yr) above the ocean basins, together with that associated with the downward isostatic displacement of lighter material, amounts to about 0.5×10^{10} W. A further 0.5×10^{10} W must then be added to account for the gravitational energy of the mountain belts which, although two orders of magnitude lower than that of other continental areas, was acquired in only 10^7 yr. The total energy involved in "visible" tectonics is thus dissipated at about 4×10^{10} W.

To the same side of the equation must also be added the energy dissipated by the drag of lithospheric plates on the viscous asthenosphere. It turns out that for shallow cells 300 km thick the shear stress involved is 34 bar and, assuming an average plate velocity of 4 cm yr^{-1} relative to the lower mantle, the rate of energy dissipation is 110×10^{10} W, or 114×10^{10} W when added to the dissipation by visible tectonics. For convection cells 1,000 km thick, on the other hand, the corresponding shear stress is 6.8 bar and the energy dissipation falls to 22×10^{10} W (26×10^{10} W including visible tectonics). In short, the negative side of the energy equation is critically

dependent on the thickness of the convection cells involved.

To balance the dissipation, three possible sources of energy are considered by Lliboutry — the convective heat engine, progressive differentiation of the crust from the mantle and residual segregation of the iron core from the lower mantle. As far as the heat engine is concerned, Lliboutry calculates that, neglecting conduction, the heat reaching the lithosphere will be 180×10^{10} W if convection cells are 1,000 km thick and $2,800 \times 10^{10}$ W for cells 300 km thick. The latter figure is much higher than the heat flux actually observed (840×10^{10} W at a depth of 30 km), which suggests that shallow convection cells are hardly possible. The figure of 180×10^{10} W, on the other hand, is well within the limits of observed heat flow and sufficient to account for drag dissipation, but is hardly in balance. However, the rate of energy release by crustal differentiation is calculated as 22×10^{10} W, which is roughly the rate required to balance the dissipation rate for convection cells 1,000 km thick—a circumstance which leads Lliboutry to regard crustal differentiation as an attractive source of energy for (deep) convection. But although the energy balance equation suggests generally that shallow convection is not possible, the energy position is not entirely clear because it appears that 840×10^{10} W could be produced by continued accretion of the core.

Nevertheless, further support for the thesis of deeper convection comes from a study of the mechanics of a three-layer model in which the upper layer representing the plate has uniform thickness and properties, is perfectly elastic, and slopes. The reason for the slope is that the energy source is supposed to produce a broad bulge in the ridge area, thus allowing the plate to slide under the influence of gravity. The second layer of the model represents the asthenosphere and has a uniform viscosity of 4×10^{20} poise, a horizontal lower boundary and an upper boundary with the same slope as the plate. The third layer, the upper mesosphere, has a viscosity of 10^{22} poise and an unspecified thickness. Both the second and third layers have lateral variations in density.

What emerges from the mathematical analysis of this model is that for shallow convection cells (less than 500 km thick) the slope of the plate is higher than observation allows. For example, for cells which are 300 km thick, the slope turns out to be 17×10^{-4} . In other words, if the model is valid, observation would seem to preclude shallow convection. On the other hand, for cells greater than 500 km thick there is no such restriction. For cells 1,000 km thick, for example, the slope is only 1.1×10^{-4} , which is credible.

Sugar and Disease

JOHN YUDKIN

Queen Elizabeth College, University of London

Professor Yudkin discusses whether the intake of dietary sugar is linked with some diseases.

THE view that sugar (sucrose) may cause disease is not generally accepted; first, because few realize the size of the contribution of sucrose to the diet in Western countries, and second, because of the widespread belief that sucrose has the same effects in the body as has any other metabolizable carbohydrate.

The average intake of sucrose in Western countries, which in the early 1700s was about 2 kg a year, is now about 50 kg a year (Fig. 1). This is usually between 15% and 20% of the energy value of the diet. In Britain, it is a higher percentage than that provided by bread and flour, or by meat, poultry and fish, or by milk, cheese and eggs. In some people, especially teenage boys, the average intake can supply up to 50% of calories.

Sucrose has a wide range of unique chemical, biological and metabolic properties¹ and an increase of sucrose in the diet, largely at the expense of starch, is not simply the replacement of one carbohydrate by another. Sucrose taken in addition to other foods already adequate in calories is likely (but not certain) to give rise to obesity: taken instead of other foods, it reduces the nutrient content of the diet, since sucrose holds the unique position of a food component that supplies calories without nutrients, that is, "empty calories". Although there is no significant prevalence of nutritional deficiency in Britain, desirable foods are displaced by sugar-rich foods, which leads to a decrease in consumption of meat and fruit. Although only limited statistics are available they reveal that these falls are associated with a rise in the consumption of foods and drinks containing sugar consistent with an increase in the standard of living and sophistication of food technology.

If we are concerned about the nutritional adequacy of our diets we should be more concerned about the displacement of nutritious foods by sugar than about the possible reduction in the nutrient content of foods by production or processing methods.

Effects of Sucrose

People eat foods that they like; palatability determines not only the amounts of individual foods eaten, but also the total amount of food eaten. Overeating is a necessary, though apparently not a sufficient, condition for the development of obesity.

Sucrose imparts to a large number of foods and drinks a taste and a texture that make them highly attractive to many people. The taste for sweetness often begins immediately after birth. Artificially fed babies almost invariably have sucrose added to their milk, rather than the far less

sweet and metabolically different lactose, and their first solid food is often made tempting with sugar. It is now accepted that a child will quench his thirst with something like a cola drink, or will have a chocolate biscuit or some other confectionery during his break or after his lunch, or indeed instead of his lunch. Much of the sugar comes combined with other components such as fat and flour, which also provide virtually empty calories. The effects are seen in the increasing prevalence of obesity, particularly in babies and young children.

While it is often difficult to induce people to take less sugar in their food and drink, obesity can be considerably lessened in those who can be persuaded to adopt this one measure.

Dental Caries

In our studies on dental caries in 15 to 18-year-olds, there was a positive correlation between the degree of dental caries and the amount of sugar taken in solid foods in those who did not clean their teeth. Those who cleaned their teeth, however, had little caries whatever their sugar consumption. In rats dental caries was much greater when the dietary carbohydrate was sugar rather than starch; degree of caries was proportionate to the amount of sugar. The cariogenic nature of sucrose seems to be because it is a better precursor of dextran than are any of the other dietary carbohydrates, and dextran is an especially good pabulum for the growth and activity of the cariogenic *Streptococcus acidophilus*.

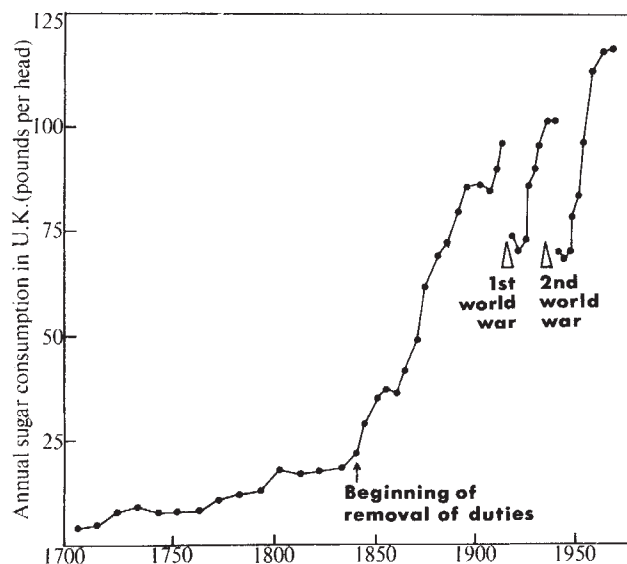


Fig. 1 Annual consumption of sugar per head of population in the United Kingdom.

Dyspepsia

Several of the patients referred to the obesity clinic at St Stephen's Hospital, London, were suffering from hiatus hernia and several others suffered from chronic dyspepsia. In many cases, treatment of their obesity with a low-carbohydrate diet resulted in a disappearance or considerable alleviation of their symptoms. The improvement occurred as soon as the patient reduced his intake of carbohydrate, even before weight reduction began.

We instituted a therapeutic trial to compare the effect of carbohydrate restriction with the effect of conventional dietary treatment of frequent small meals with avoidance of spicy and fried foods. The subjects were men and women with a variety of conditions in which the main symptom was chronic dyspepsia of at least six months' duration; in many the symptoms had persisted for several years. The conditions were diagnosed as hiatus hernia, gastric and duodenal ulcers, and "X-ray negative chronic dyspepsia" (dyspepsia without X-ray evidence of ulceration). Patients were instructed to take either the low carbohydrate diet or the conventional diet for three months and to take the other diet for a second three months. The diets were prescribed and checked by a nutritionist who was not concerned with clinical assessment, and the physician who made regular clinical assessment did not know which treatment the patient was receiving. After six months' observation, the results were classified according to improvement.

Forty-one patients completed the period of observation (24 men and 17 women). Two said their symptoms were worse on the low-carbohydrate diet, 11 said they were equally improved or equally unaffected by the two diets, and 28 patients said they were better with the low carbohydrate diet than with the conventional diet (Table 1). There was no obvious difference in response between men and women, or between patients with different conditions.

Table 1 Chronic Dyspepsia Treated with Low Carbohydrate Diet and Conventional Diet

Diagnosis	No. of patients	Effects of low carbohydrate diet	Better	Equal	Worse
Hiatus hernia	9	8	1	0	
X-ray negative	22	13	8	1	
Duodenal ulcer	8	5	2	1	
Gastric ulcer	1	1	0	0	
Gall stones	1	1	0	0	
Total	41	28	11*	2	

* 5 equally good; 6 equally bad.

Gastric secretion was examined by test meal in young male volunteers before and after a diet high in sucrose. 150 g of sucrose was substituted for an equivalent amount of the starch in their usual diet. After two weeks on this diet, a pectin test meal given before breakfast revealed an increase in acidity of about 20%, and an increase in pepsin secretion of nearly 200%; these results suggest that sucrose is involved in the production of chronic gastritis, and perhaps also gastric and duodenal ulcer. We do not know how sucrose produces its effect on gastric secretion, but two possibilities are the high osmotic pressure exerted by sucrose, and the increased secretion of adrenocortical hormones.

Seborrhoeic Dermatitis

Men and women with seborrhoeic dermatitis have been shown² habitually to consume significantly more sugar than those of the same age who do not have the disease (170 and 110 g/day respectively). We then instructed patients to abstain from dietary sugar. Results of this trial so far suggest that the treatment is beneficial in many patients (Table 2). Although little experimental work has been done

Table 2 Effect of Sucrose-free Diet on Patients with Seborrhoeic Dermatitis

Treatment	Total	Assessment after 1 yr	
		No. of patients Cured	No change
Diet	8	7	1
Control	11	2	9
P value		<0.01	

on the effects of sucrose on the condition of the skin in man or laboratory animals, we have observed a striking dermatitis in pigs fed sucrose for several months; the nature of this now awaits detailed histological examination.

Eyes

The suggestion made 25 years ago³ that protein deficiency may affect refraction of the eye has never been confirmed, but it has been shown that a protein-deficient diet that contains sucrose produces an irreversible myopia in growing rats. Rats after 202 days on a diet containing starch had an average ocular refraction of +0.59, whereas those on a diet containing sucrose had an average of +0.10. It is possible that this myopia is a reflexion of the level of blood glucose; in young men, a sucrose-rich diet taken for two weeks produces hypermetropia rather than myopia which may be related to the lowering of fasting blood glucose and an improvement in glucose tolerance.

Sucrose and Protein Deficiency

Rats fed diets marginally low in protein suffer a setback in growth when sucrose replaces some of the dietary starch. We have shown that the sucrose reduces the utilization of protein in these conditions (Table 3). This has relevance to the occurrence of kwashiorkor in developing countries, where increasing urbanization exposes children to diets low in protein but also containing sucrose.

Table 3 Nitrogen Retention in Rats Fed on Sucrose

Experiment	Duration days	Diet	N retention, mg
1	24	Starch	17
		Sucrose	2
2	14	Starch	17
		Sucrose	-2
3	48	Starch	6
		Sucrose	-6

Diabetes

It has been suggested that diabetes mellitus may become manifest only after an environmental determinant has acted for 20 years or so. There was a positive correlation ($r=0.73$) between the incidence of the disease and the sucrose consumption 20 years earlier. In rats a diet with sucrose taken for several weeks reduces glucose tolerance. In human beings a short period on a high sugar diet improves glucose tolerance but a long period reduces it. The level of plasma insulin in rats is decreased; in pigs and in some human volunteers there is at least a temporary increase in plasma insulin (Tables 4, 5).

Ischaemic Heart Disease

In rats, sucrose produces an increase in plasma triglyceride, and occasionally also an increase in cholesterol. Although atheroma has been reported⁵ in rats fed sucrose, most strains are resistant to the production of atheroma. Dietary sucrose, however, produces increases of triglyceride and cholesterol in the aortic wall.

It also increases the activity of many enzymes in the

Table 4 Plasma Insulin ($\mu\text{U}/\text{ml.}$) in Litter Mate Pairs of Pigs Fed on Diets with Starch or Sucrose

Pair	Starch diet	Sucrose diet
1	17	66
2	9	29
3	4	9
4	6	8
5	11	13
6	6	8
7	6	36
Mean	8.5	24.4

Table 5 Plasma Insulin ($\mu\text{U}/\text{ml.}$) in 23 Men on High Sucrose Diet for 2 Weeks

Diet	17 subjects			6 subjects		
	0'	30'	120'	0'	30'	120'
Normal	16	61	24	15	57	25
High sucrose	20	67	29	33	120	71
Normal	23	66	27	24	61	25

Insulin measured in fasting blood, and at 30 min and 120 min after 50 g oral glucose, before, immediately after, and 14 days after high sucrose diet.

rat. In the liver there are great increases in the activities of pyruvate kinase and in the fatty acid-synthetase complex; the synthetase complex in the adipose tissue is considerably diminished. Insulin levels are decreased by sucrose, and glucose tolerance is diminished. The liver and kidneys are often enlarged, and sometimes there is considerable accumulation of fat in the liver. DNA assay shows that the enlargement is due not only to hypertrophy but also to hyperplasia. In animals fed sucrose from 24 days, the adrenal glands rapidly enlarge. In the liver the enlargement persists into adult life but the adrenals are enlarged only in the first few weeks, suggesting that sucrose accelerates maturation of the adrenal glands.

Pigs fed a diet with sucrose developed a decrease in plasma albumin and a rise in plasma insulin. After 4–5 months, the skin had an overall red appearance, with staring hair.

In cockerels diets containing sucrose have produced an accumulation of lipid in the aorta. In White Leghorns 46% of the intimal surface was stained by Sudan IV; this was proportional to the rise in the level of plasma cholesterol. Cockerels on the control diet show staining of less than 1% of the area. In a Rhode Island–Light Sussex cross, definite atheromatous lesions were seen in experimental birds but not in controls.

In young men on diets with higher amounts of sucrose and lower amount of starches than their habitual diets, an increase in the level of triglyceride was shown after two weeks. One third also showed a substantial rise in plasma insulin, in body weight and in platelet stickiness. The platelets also showed the same change in electrophoretic behaviour as is found in atherosclerotic patients. In a second experiment, all subjects showed a rise in cholesterol level, and an improvement in glucose tolerance. Other workers⁶ have shown that a longer time on such a diet results in a deterioration of glucose tolerance. We have found that the rise in plasma insulin level in some subjects is accompanied by a much greater rise in plasma 11-hydroxycorticosteroid, and we believe that this may well be the key factor in atherogenesis. That the increase is found in some subjects only may indicate a factor of susceptibility to the atherogenic properties of sugar.

A high level of insulin occurs in coronary disease and in several conditions associated with it; obesity, cigarette smoking, peripheral vascular disease, and maturity onset diabetes. On the other hand, physical activity and loss of weight in obese patients, both of which are regarded as

measures that reduce the risk of coronary disease, cause a lowering of insulin level. This, however, does not necessarily mean that an increase of insulin is the first stage in the atherogenic process when dietary sucrose is high. As sucrose causes an accelerated maturation of the adrenal glands and a considerable rise in the corticosteroid content in fasting blood, the atherogenic process may be mediated through the adrenal glands rather than through insulin. The multiple changes that occur in occlusive atherosclerotic disease are likely to be the results of interrelated hormonal changes, induced by sucrose and other agents.

Gout

Subjects with gout tend to take significantly more sugar than do matched control subjects, and although there are no detailed studies with sucrose, dietary fructose increases the level of plasma uric acid.

Sucrose, Hormones and Enzymes

A third reason for the lack of acceptance of dietary sucrose as a potent factor in the causation of disease may be apparent, that is, the disparate nature of some of the conditions I have described—obesity, dental caries, dyspepsia, seborrhoeic dermatitis, and coronary disease. Sucrose does, however, have several properties that distinguish it from all other food components; it contributes far more than any other constituent to the osmotic pressure of our food; it profoundly affects hormone secretion in the body; and it induces considerable and rapid changes in the activity of several tissue enzymes. Sucrose differs radically from other dietary carbohydrates, especially from starch which is our other major carbohydrate, but which is being displaced from our diet by sucrose. It is widely accepted that there is a relationship between obesity, diabetes mellitus, and coronary disease. There is evidence also of a relationship between gout, peptic ulceration and coronary disease. Each of these diseases has several causes, and if dietary sucrose is one of them, one would expect a slight relationship between all these diseases.

There is concern about the possibility that food may contain hormones such as the oestrogens once used in animal feeds. These do not significantly affect the levels of hormones in the flesh of the animals, and they certainly do not affect the levels in the blood or tissues of the consumer; sucrose, on the other hand, can cause a rise of 50% in the level of insulin in fasting blood, and a rise of 300%–400% in the level of corticosteroids. Future work on the effects of dietary sugar may reveal more important metabolic effects, but the one property of sucrose that today most seriously calls into question the general assumption that it is a completely innocuous component of our diet, is its effects on hormone levels.

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Differentiation *in vitro* of Mouse Embryos beyond the Implantation Stage

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Detailed examination of mouse embryos which are implanted *in vitro* on reconstituted collagen shows that they survive and differentiate normally for 14 days.

ONE of the greatest gaps in our knowledge of the process of implantation is the lack of a detailed description of the timing and sequence of events. Now that mouse embryos have been successfully implanted *in vitro* on reconstituted rat tail collagen¹, the development and the sequence of events immediately after implantation can be elucidated. In particular, various physical and chemical effects on the developing embryo can be studied at the stage of implantation.

Until now, it has been possible to cultivate mouse embryos *in vitro* from the fertilized one-cell ovum stage only up to the end of the cleavage stage^{2,3}, when implantation occurs in mice. Further development was thought to depend upon contact with the living uterus⁴. Several workers have reported that in tissue culture even with a collagen substrate^{5,6} the inner cell mass failed to differentiate into endoderm and ectoderm, and degenerated. It is clear, however, that it is possible to induce the mouse embryo to develop *in vitro* for almost one half of the gestation period¹.

Here I describe the very early differentiation *in vitro* of the mouse embryo immediately after implantation and discuss the possible factor(s) which are required for its development. The later stage, to the stages of 10 somites and blood circulation in the yolk sac, will be described elsewhere.

Mouse blastocysts of 3.5 days of gestation were collected and prepared according to established procedures⁷. Random bred female mice, 7 weeks old, were superovulated by injections of 5 IU of pregnant mare serum gonadotrophin, followed 48 h later by 5 IU of human chorionic gonadotrophin, and caged overnight with males of proven fertility. Insemination was verified the following morning by the presence of a copulatory plug in the vagina. Blastocysts were collected by flushing the uterine horns with culture medium approximately 83 h after the injection of gonadotrophin. Flushings from several mice were collected and pooled in an embryological watchglass, after which the flushed blastocysts were washed and transferred to fresh medium. Groups of fifty and sixty blastocysts were

placed in 50 mm plastic Petri dishes coated with reconstituted rat tail collagen and containing Eagle's minimum essential medium supplemented with foetal calf serum, and incubated in a humidified atmosphere of 5% CO₂ and 95% air at 37° C.

On the first day of incubation, the blastocysts began to shed the zona pellucida, after which they became sticky and lay flat on the surface of collagen with the inner cell mass on one side and the abembryonal pole on the other. Thereafter, the trophoblastic cells either transformed into giant cells on the

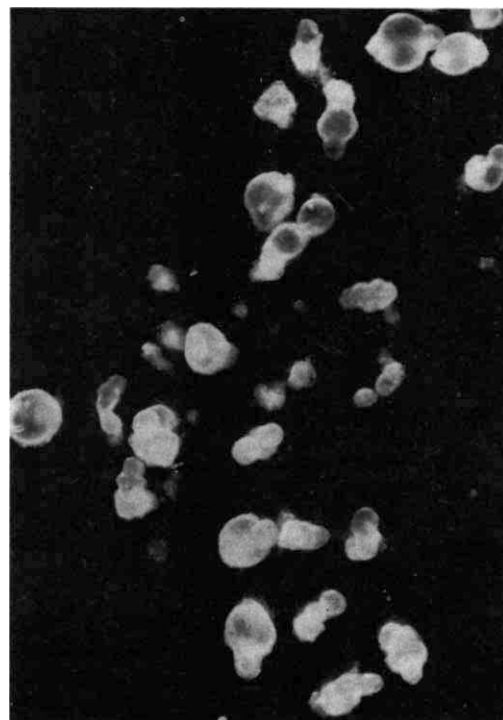
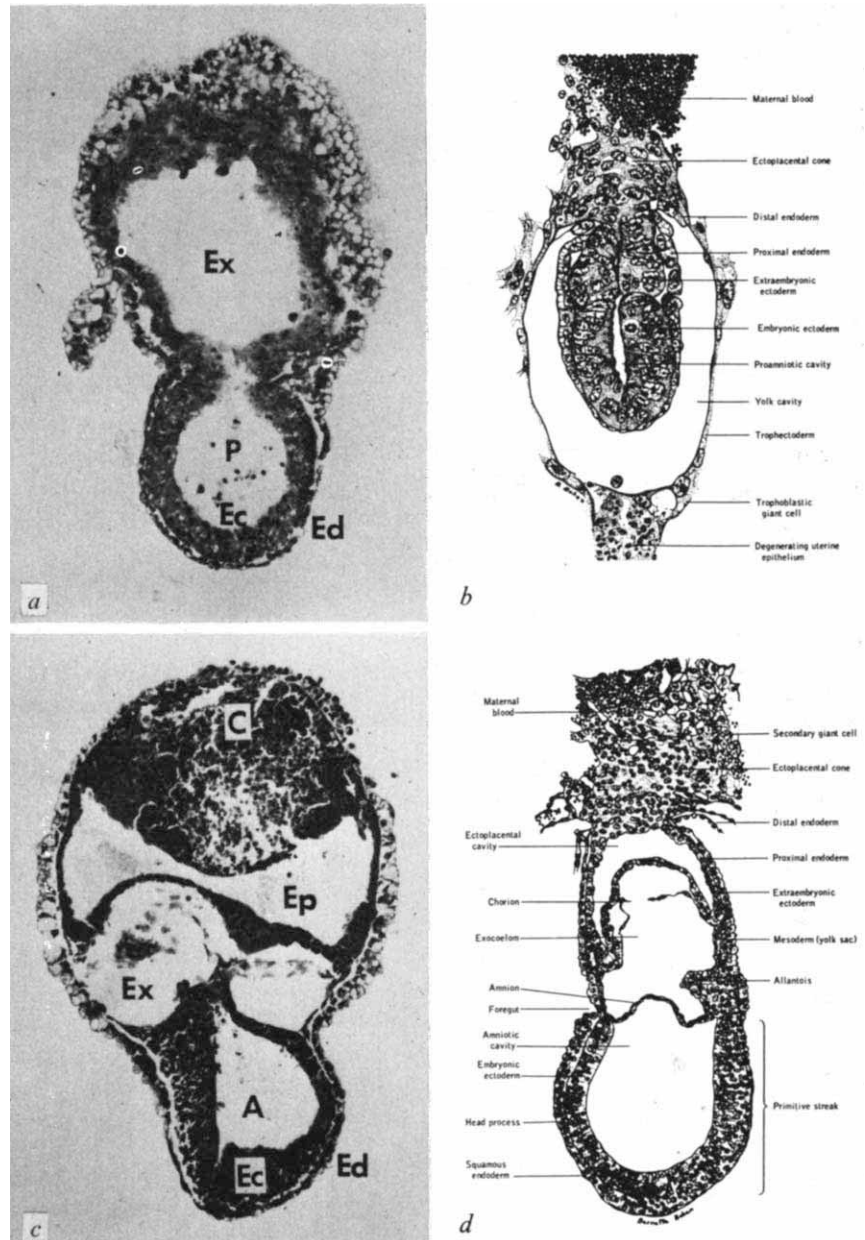


Fig. 1 Oblique light illumination of mouse embryos developed for 6 days in tissue culture in 50 mm plastic Petri dishes from blastocysts of 3.5 days of gestation. Most embryos form a dumbbell shape consisting of the embryonic and extraembryonic regions ($\times 14$).

surface of the collagen, or invaded the underlying collagen. Thus the inner cell mass was firmly fixed on the surface of the collagen. The invaded trophoblasts and those which remained on the collagen surface did not proliferate but eventually degenerated. In contrast, the inner cell mass grew rapidly and differentiated with a definite organized structure.

The proportion of mouse embryos which did develop further varied from 10 to 100%, with an average of 15–20%. A group of mouse embryos after 6 days of development in Petri dishes is shown in Fig. 1. Most of the egg cylinders were dumbbell-shaped and consisted of two parts: embryonic and extra-embryonic.

Fig. 2 Histological sections of two mouse embryos (*a* and *c*) shown in Fig. 1 were compared with that developed *in vivo* (*b* and *d*). Mouse embryos were fixed with Helley's solution for 1 h and embedded in 'Paraplast'. A 6 μ m section was stained with haematoxylin and eosin. *b*, 6 days gestation; *d*, 7 days 6 h gestation, from *Biology of the Laboratory Mouse*, by Snell and Stevens (Green, E., editor), copyright 1966. Used with permission of McGraw-Hill Book Company. A, Amniotic cavity; C, ectoplacental cone; Ec, ectoderm; Ed, endoderm; Ep, ectoplacental cavity; Ex, exocoelom; P, proamniotic cavity.



On the fifth day of cultivation, the endoderm and ectoderm protruded from the surface of the inner cell mass to form the egg cylinders. At the same time, the extraplacental cone spread into the underlying collagen, leaving the egg cylinder floating in the culture medium. This step seems to be critical for the development of the embryo after implantation. The majority of unsuccessful embryos cultured *in vitro* remained apparently alive in the culture medium as an undifferentiated inner cell mass for more than 2 weeks before degenerating.

The degree of differentiation *in vitro* was compared with that *in vivo*^{8,9}. Figs. 2 (*a*) and (*c*) correspond to mouse embryos developed *in vivo* for 6 days and for 7 days 6 h gestation, respectively. The trophoblasts did not proliferate *in vitro*, so the mouse embryos which developed had no parietal endoderm; instead the visceral endoderm developed over the surface of the whole embryo surrounding the extraplacental cone.

The mouse embryo differentiated *in vitro* had a consistent polarity in relation to the underlying collagen, with the ectoplacental cone spreading into the underlying collagen and the

egg cylinder floating in the culture medium. The polarity of mouse embryo is determined immediately after implantation, according to evidence from fusing two inner cell masses to form one whole mosaic mouse of normal size¹⁰, and by the analysis of hair follicles in allophenic mice¹¹. The direction of endoderm and ectoderm extended from the inner cell mass determines the polarity in differentiation *in vitro*. One explanation may be that the polarity of inner cell mass is directed by the underlying collagen.

A small proportion of the naked blastocysts floated in the culture medium for several days without attaching to the underlying collagen or undergoing cytodifferentiation.

Attachment to the surface, however, is a requirement for the development of the mouse embryo only in the early stage of differentiation. Once the embryos formed endoderm and ectoderm and a proamniotic cavity which accumulated liquid, the whole embryo tended to float in the culture medium. Some embryos detached from the underlying collagen and moved freely in the medium, but development of the embryo continued up to the stage of formation of 10 somites and a beating heart. Attachment of the embryo is therefore not required for the later stages of development.

The mouse embryos grown *in vitro* are egg cylinders or embryos proper, but they lack trophoblast, Reichert's membrane and parietal endoderm. The process of development *in vitro* appears to follow the normal process of differentiation. Once the differentiation barrier immediately after implantation is overcome, the factor which regulates the sequence of differentiation is intrinsically in the embryo rather than being supplied by the mother.

The difficulty many other workers have found in developing mouse embryos *in vitro* without contact with the living uterus is apparently in inducing the differentiation of endoderm and ectoderm from the inner cell mass. Subsequent differentiation may be caused by a chain of events similar to that of oviparous animals.

Most commercially available calf serum tested in our laboratory did not induce the differentiation of the inner cell mass into endoderm and ectoderm, which seemed to be a function of some foetal calf serum. Our preliminary results suggest that the active component in serum contains non-dialysable macromolecules. In this connexion, it has been well established that both oestrogen and progesterone are essential for the implantation and subsequent development of mouse embryos¹².

Blastocyst implantation does not take place in mated and ovariectomized mice. By administration of oestradiol in addition to progesterone in such ovariectomized mice, however, a high percentage of implantation sites were produced.

It is not clear at the present time whether the active component(s) in foetal calf serum is a normal serum component or the steroid hormone complexed with steroid binding globulin¹³, or the product of steroid target cells released from the maternal tissues such as the uterine specific glycoprotein^{14,15}.

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Flake Tectonics and Continental Collision

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The concept of crustal flakes can explain several of the features of complex plate margins.

HERE I show that when two continents collide it is possible for large sheet-like masses of material ("flakes") to be sheared from the top of one of them and driven over the other for more than 100 km. This process has widespread implications for the origin of allochthonous basement thrust sheets and for patterns of contemporary collision zone seismicity which may be

expected to become diffuse through the dominance of movements on low angle crustal faults. Laubscher¹ has independently suggested that a process of this kind has operated in the Central and Western Alps. The arguments presented here arise from studies in the Eastern Alps and my conclusions are then applied in a more general way to destructive plate margins.

I shall first consider the evidence for the existence of flakes. In the Eastern Alps a pre-Mesozoic metamorphic basement complex (Fig. 1, unit *A*) has been overridden more than 100 km by an allochthonous thrust mass of pre-Upper Palaeozoic metamorphic rocks (unit *C*) moving from the south-west². Between the two lies a highly deformed and stratigraphically disordered sequence of Mesozoic (and locally Palaeozoic) metasedimentary rocks (unit *B*). These relationships are established in an area of high relief and good exposure and

and diaphoresis may be associated with the thrusting. The thickness of unit *C* is uncertain but it probably nowhere lies between 4 km and 12 km. Thus not only is the overriding "plate" much thinner than commonly believed in plate tectonics (say 60 to 100 km), but is less than half the thickness of normal continental crust and contains lithologies and mineral assemblages (including abundant primary hydrous phases) characteristic of the upper half of the continental crust. I conclude that although all possible geological evidence for a suture zone between different plates is present, the geological evidence itself precludes the possibility that *C* can be a full plate in the usual sense of the word. It seems that a thin upper crustal flake has been detached from the southern plate by some process which has allowed it, and only it, to override the continent to the north.

Lithospheric Split

What happened to the lower crust and upper mantle which originally underlay unit *C*? Together they must have comprised a coherent slab of material more than 100 km long and some 50 to 60 km thick, and the geometrical constraints imposed by the surface geology already described, together with volume considerations, mean that this slab must have descended into the mantle along a zone inclined to the north (Fig. 1). The southern edge of the north European continent appears to be a wedge which splits the advancing continental lithosphere into a thin upper flake that overrides it and a thick lower slab that dips beneath it.

I therefore postulate not only the former existence of an area of oceanic crust between continents *A* and *C* but also an oceanic trench with a northward dipping subduction zone along the southern margin of the northern continent (*A*).

Closure of the ocean by destruction of oceanic lithosphere and relative northward motion of the southern continent finally resulted in contact between the two continental masses and the splitting of the southern one. As the upper flake overrode the northern block it dragged with it a severely deformed mélange of trench and other ocean floor deposits trapped between the blocks. Overriding continued to the extent of at least 100 km before motion ceased, and the present disposition of units was reached. Metamorphic mineral parageneses in the mélange rocks of unit *B* indicate that the crustal thermal gradient rose to about $40^{\circ} \text{ km}^{-1}$ during the mid-Tertiary and there has been extensive Miocene mineralization. Both observations are consistent with anomalously high heat flow expected in an area overlying an inclined mantle slipzone; calc-alkaline volcanicity is missing but calc-alkaline intrusives (the peri-adriatic intrusives⁵) intrude *C* as shown in Fig. 1.

The dynamics of flake generation can at present be interpreted in only the most general way. I shall make two assumptions; first, that oceanic lithosphere (that is, crust and coupled upper mantle) descends into the mantle in island arc areas because it is cooler and on average more dense than underlying mantle material⁶; second, that continental lithosphere does not participate in subduction because continental crust is both thick and of low density and its underlying upper mantle has a stable density distribution.

When a continental area approaches a subduction zone through the destruction of intervening oceanic lithosphere, one part of the continent will arrive at the subduction zone before adjacent areas (Fig. 2) unless there is a remarkable coincidence of shapes. Body forces at *X* should then resist further subduction, whereas elsewhere on the plate margin (*Y* and *Z*, for example) body forces favour continued subduction. Insofar as *X*, *Y* and *Z* are all part of the same coherent plate, some kind of mechanical compromise must be reached at *X* until contact is made at sufficient points between continents for the plate boundary to become locked and subduction to cease.

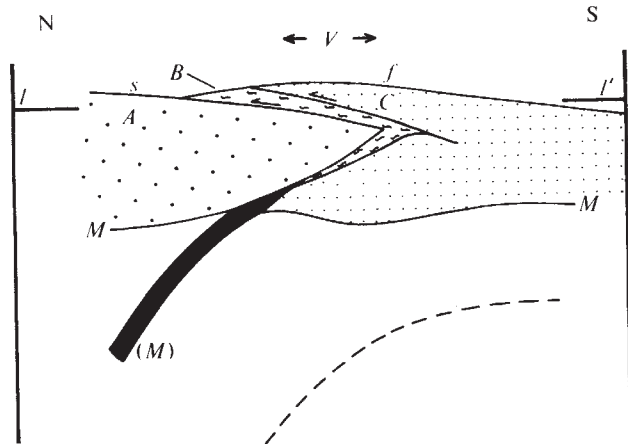


Fig. 1 A geological cartoon representation of gross geological relationships in the Eastern Alps. That part of the section above the line $I-I'$ is well established, that below the line is inferred. Unit *A* represents the Bohemian massif and its southward continuation into the Hercynian gneisses of the Tauern. The Northern Calcareous Alps, Helvetic Zone, Flysch Zone, Grauwacken Zone and autochthonous Mesozoic cover within the Tauern Window are omitted. Unit *B* represents the Peripheral Schieferhülle², and unit *C* the Altkristalline Decke. *s*, Salzburg; *f*, the Italian frontier; *M*, the M discontinuity; black, subducted oceanic crust; *V*, per-Adriatic intrusive activity; ---, base of the lithosphere.

have been known for many years³. Radiometric dating and petrological and stratigraphic studies show that units *A* and *C* have completely different geological and thermal histories and were probably not in their present relationship earlier than the Miocene^{1,2}. Unit *B* is, however, in large part a mélange of pelagic metasediments and occasional metavolcanics which could have been oceanic in origin^{2,4}. I conclude on these grounds and on the evidence of rational geological relationships that although unit *A* represents the southward continuation of a north European continental massif, unit *C* belonged to a separate southern continent or microcontinent comprising at least Italy (Italy and unit *C* being apparently continuous at present) and that units *A* and *C* formerly belonged to different plates.

If this model is correct the lowest rocks in unit *C* represent the base of an overriding plate. These, however, are a series of rather sheared and diaphoritized schists and gneisses which pass upwards into a complex of medium grade metasedimentary rocks interfolded with granodioritic gneisses. Field and radiometric studies leave no doubt that the folding and prograde metamorphism is pre-Mesozoic and that only the basal shearing

In the case of the Eastern Alps the mechanical compromise involved splitting of the lithosphere within the continental crust. This splitting may have been partly associated with the arching of the lithosphere which occurs as the downturn into the trench is approached. Because the continental crust stands more than 5 km higher than oceanic crust, however, mechanical locking could occur as the continental crust enters the subduction zone. I suggest that a low angle crustal split propagated backwards from this locking point and that flake separation then occurred (Fig. 3). A separation of the upper third of the continental crust would have the effect of reducing the total buoyancy of the subducted crust by nearly a half.

Other Flakes

I shall now consider briefly two of the many other geological situations where flake formation has occurred. The Insubric Line⁶ of the Central and Western Alps appears to be the westward lateral continuation of the same crustal splitting surface discussed above. In the Central Alps, however, the split occurs just below the M discontinuity. It seems that a situation further back in the advancing plate is exposed, and that as the split propagated it also moved downwards in the crust so that, in the Central Alps, the flake comprises the whole of the continental crust. Thus the Insubric Line, originally a thrust fault, has been steepened by vertical movements that occurred after splitting.

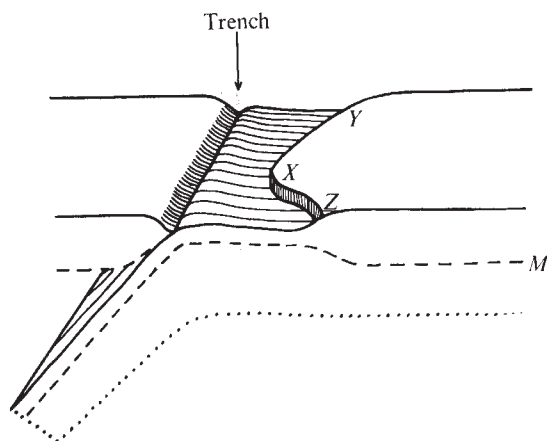


Fig. 2 Schematic representation of an irregular continental margin (ZXY) approaching a trench at a continental margin. / / / , Oceanic crust; ---, M, discontinuity; . . . , base of lithosphere.

A second example is to be found in the Lower Himalayas where Gansser's section⁸ shows extensive allochthonous units of basement schists and gneisses overlying unmetamorphosed sedimentary sections which in turn overlie metamorphic basement. The sedimentary sections in many cases contain tectonic intercalations of ophiolitic rocks of presumed oceanic origin.

Unless the opposed continents happen to match very closely, the proposed model has the general implication that zones of collision between continents should be characterized by zones of overthrusting and flake formation alternating with pockets of old ocean floor where the continents failed to meet. It is only in such areas as these that there is some hope of finding relatively undisturbed records of pelagic deposition in the

Palaeozoic. In a general way the whole Alpine-Himalayan belt may be regarded as a collision margin of this kind. It is to be expected that in some cases flakes may become detached from the plate from which they were derived. Where plate motions continue there is the possibility of forming more than one flake from the same plate or of breaking existing flakes into smaller pieces. The pattern of contemporary seismicity expected in such circumstances is likely to be very complex with the larger scale motions of the principal parts of the plates reflected at the surface in jostling of crustal flakes over and against each other. Such a model could well explain some aspects of contemporary Mediterranean seismicity⁹.

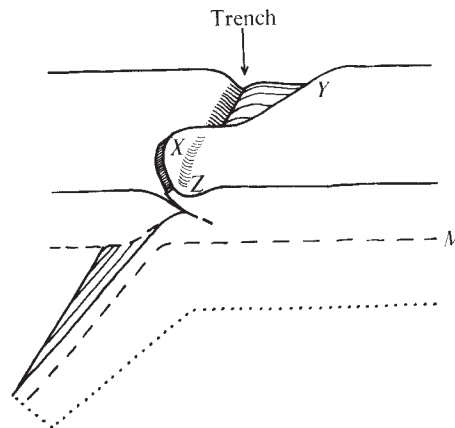


Fig. 3 Formation of a crustal flake after continental collision; conventions as in Fig. 2.

In other situations too, thin crustal flakes can become detached from the underlying plate along plate margins and move with respect to each other. The contemporary pattern of movements recognized in southern California by Anderson¹⁰ is very difficult to interpret if this is not the case; the seismicity of the area is associated with movements on crustal faults which must completely bound small detached flakes which slip with respect to each other in response to motion of the more coherent (but probably less rigid) lithosphere beneath.

Thus the concept of crustal flakes provides a mechanism for the generation of large scale thrust sheets of basement rocks, it suggests an explanation for the pattern of crustal seismicity along various complex plate margins and it indicates the plate margins themselves may in some situations be obscured by relatively thin flakes which appear to have moved on thrust faults dipping in the opposite direction to the underlying subduction zone.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Trace Element Geochemistry of Apollo 16 Soil 68501

THE Apollo 16 lunar samples were obtained from the first site remote from the maria basins (landing site $9^{\circ} 00' 01''$ S; $15^{\circ} 30' 59''$ E). The Descartes region is in typical highlands terrain, saturated with large craters. Two separate formations, identified from photographic mapping, were sampled. These were the Descartes Formation, comprising the hilly terrain, and the Cayley Formation, making up the smoother lower lying plains. The sample reported on here is a soil from station 8 of the traverse (EVA 2) located on a ray from South Ray Crater.

The geological interpretation¹ suggests that all the material collected at station 8 represents ejecta derived from South Ray Crater. This is a young crater which has excavated material to depths of several hundred feet in the Cayley Formation (and possible underlying material). The fresh-looking ejecta dominate the southern part of the traverse area, west of Stone Mountain. The soil sample from station 8 is thus probably representative of the Cayley Formation (or underlying highland material) and has minimal contributions from other parts of the Moon. Because South Ray Crater is young, contributions to the soil derived from later impacts on maria must be small. The large amount of Cayley Formation excavated by South Ray Crater effectively dilutes the mare component present before impact, so the present sample should be typical of Cayley Formation highland material.

We have analysed sample 68501,46, a 2 g sample of soil (<1 mm), by spark source, mass spectrographic and emission spectrographic techniques similar to those used on Apollo 12 and 14 lunar samples²⁻⁵. In addition to a bulk sample of the soil, 10 mg of plagioclase, separated by handpicking, was analysed. The data are given in Table 1. Precision, expressed as relative deviation, is $\pm 5-10\%$. We believe that our accuracy, as judged from comparison with data from other workers for Apollo 12 and 14 samples, is satisfactory.

Nickel (420 p.p.m.) is a factor of two greater than most soils analysed previously, and we attribute this to a higher meteoritic component. Metallic fragments with meteoritic compositions are also more common. This component can scarcely be derived from post-South Ray Crater bombardment. If the sample is representative of the Cayley Formation, as argued above, then this increased meteoritic component may be indigenous (pre-South Ray Crater) and derived from the early (pre-Imbrium) highland cratering. That is not consistent with the geological interpretation of the Cayley Formation as a volcanic constructional unit, but agrees with the view that it represents pre-Imbrium crust thoroughly mixed by cratering. The alternative explanation, that the excess Ni comes from the meteorite which produced the South Ray Crater, can only be evaluated by analyses of further soil samples remote from South Ray ejecta.

The general similarity between the elemental abundances reported for this highland sample with those reported from samples from earlier missions is striking. The same distinctive chemical features which distinguish lunar geochemistry are present. For example, there is a marked europium depletion. The K/U ($\sim 1,600$), Zr/Nb (15), K/Ba (5.5) and Cr/V (37) ratios

are all typically lunar. Differences from maria soils include the higher Sr content and lower Eu depletion, representing an increased plagioclase content, lower total rare earths and lower amounts of the ferromagnesian trace elements Cr, V and Sc.

The Apollo 16 68501 rare earth pattern is shown in Fig. 1, compared with those from Apollo 11, 12 and 14 soils²⁻⁴. The pattern for the plagioclase separated from the Apollo 16 sample illustrates the striking relative Eu enrichment. We also note the uniform increase toward the light rare earth (La), an effect attributable to the increasing ionic radius. The similarity between the ionic radii of divalent strontium and europium accounts for the concentration of the latter element in plagioclase.

The rare earths in the soil sample (when normalized to chondrites in Fig. 1) show the typical lunar flat pattern, parallel to the chondritic abundances, for the heavy REE (Gd-Yb), and a smooth increase from Sm to the largest REE, La. The Eu depletion measured as Eu/Eu^+ , where Eu^+ is the calculated abundance for no depletion, is 0.61. This pattern and the REE abundances are identical to those of several samples from the Apollo 15 site (Hadley-Apennines), about 900 km north-west. These include soils 15301, 15471 and several breccias from station 7 (for example 15459) on the Apennine front. But those Apollo 15 samples contain higher amounts of Cr, V and Sc.

A very close match to the composition of the Apollo 16 soil is obtained by a 60/40 mix of the white and black components of the Apollo 15 breccia 15455 (Fig. 2). Data are given in Table 1 for the white (feldspathic) and black (basaltic) components, and for the composition resulting from the 60/40 mix.

The only discrepancy between the two compositions lies in the higher nickel and cobalt contents in the Apollo 16 soil. The excess amounts are 320 p.p.m. and 16 p.p.m., respectively, giving an Ni/Co ratio of 20. This value is typical of stony meteorites, but a little higher than the typical ratio of 16 for iron meteorites⁷. We attribute the excess Ni and Co to

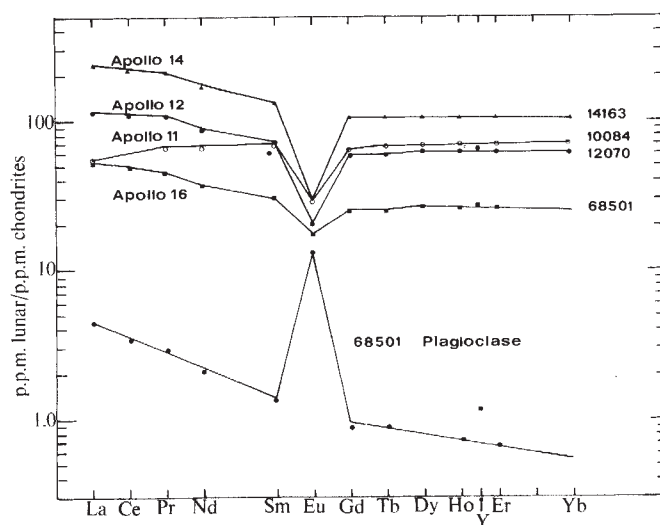


Fig. 1 Rare earth element abundances normalized, element by element, to chondritic abundances¹¹. Note the lower degree of europium depletion in the Apollo 16 sample. Apollo 15 soil 15301 from station 7, Apennine front, has a pattern closely similar to the Apollo 16 soil.

Table 1 Analytical Data for Apollo 16 Soil Compared with Apollo 15 Breccia 15455 and an Apollo 16 Plagioclase Separate

	Method †	A *	B *	C *	D *	E *
		68501, 46 Total	15455, 0.6C 0.4D	15455, 20 White	15455, 14 Black	68501, 46 Plagioclase
Cs	M	0.09	0.06	—	0.16	—
Rb	M	2.3	—	—	2.7	0.40
Ba	M	185	184	60	370	27
Eu	M	1.29	1.50	1.3	1.80	0.97
Pb	M	2.2	1.8	1.0	3.0	0.40
Sr	M	170	218	270	141	225
La	M	15.7	14.4	2.9	31.8	1.34
Ce	M	41.5	36.4	6.7	81	3.0
Pr	M	5.54	5.15	0.92	11.5	0.36
Nd	M	21.6	20.8	3.55	46.8	1.22
Sm	M	6.32	5.63	0.85	12.8	0.30
Eu	M	1.29	1.70	1.63	1.80	0.97
Gd	M	7.57	6.75	0.92	15.5	0.26
Tb	M	1.23	1.04	0.14	2.41	0.05
Dy	M	8.35	6.89	0.82	16	—
Ho	M	1.92	1.60	0.17	3.76	0.05
Er	M	5.45	4.46	0.44	10.5	0.14
Tm	M	0.75	—	—	—	—
Yb	M	4.95	4.19	0.38	9.9	—
ΣREE		122	109	19.4	244	7.7
Y	M	49	40	4.8	93	2.2
Th	M	2.45	2.25	0.22	5.31	—
U	M	0.63	0.58	0.05	1.37	—
Zr	M	220	228	60	480	170
Hf	M	4.0	4.1	0.17	9.95	—
Nb	M	14.9	13.8	0.93	33	0.60
W	M	0.11	0.12	—	0.31	—
Cr	E	1,000	985	440	1,800	—
V	E	27	25	16	39	—
Sc	E	6	5	—	13	—
Ni	E	420	81	12	184	—
Co	E	34	15	10	22	—
Cu	E	4.5	2.1	1.3	3.3	—

* Column A, Apollo 16 soil; columns B, C, D, Apollo 15 breccia; column E, Apollo 16 plagioclase separate. Data in p.p.m.

† M, Spark source mass spectroscopy; E, emission spectroscopy.

a meteoritic component, less evident at the Apennine front, where samples may be derived from several km deeper in the crust. The layering exposed on Silver Spur⁸ at the Apollo 15 site may also be taken as evidence of less cratering activity in the Apennine highlands.

The overall close similarity in composition between the Apollo 15 black and white breccia (15455) and the Apollo 16 Cayley

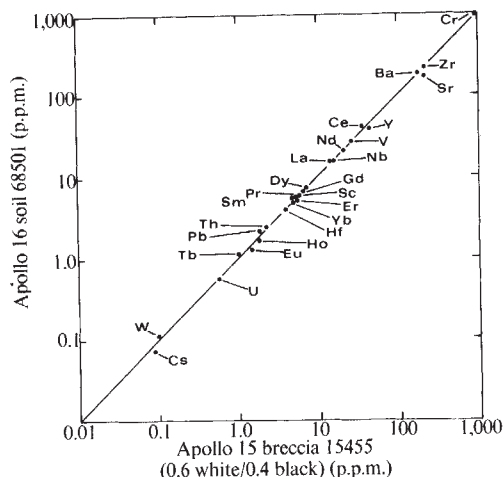


Fig. 2 Comparison of the element abundances in Apollo 16 soil (68501) with those in a 60/40 mix of white and black components of the Apollo 15 breccia 15455. Points lying on the 45° diagonal line indicate equality of composition.

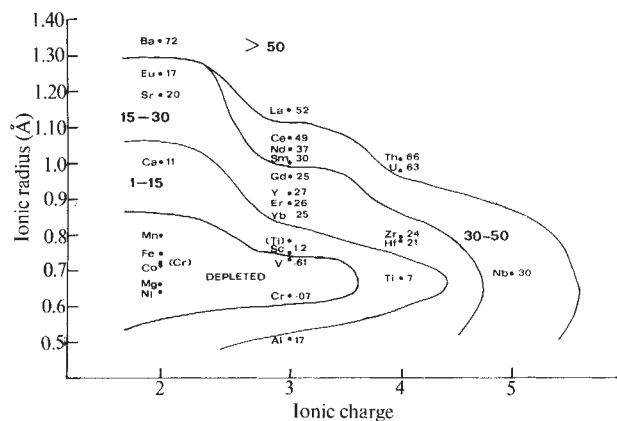


Fig. 3 Relative enrichment and depletion of involatile elements in Apollo 16 soil 68501,46 relative to abundances in Type 1 carbonaceous chondrites⁷. Contour lines separate differing degrees of enrichment. Note the progressive enrichment as ionic radius and/or valency differ from Mg^{2+} and Fe^{2+} .

Formation soil raises interesting questions. The samples are 900 km apart and probably come from depths differing by some km. Thus, the sample may be typical of wide areas of the highlands. The general similarity of the REE pattern with many of the Apollo 15 breccias from the highland station 7 encourages this view.

The orbiting XRF experiment⁹ on the Apollo 16 Command Module indicated an Al/Si ratio of 0.58, a typical highland value, and further evidence that the Descartes region composition may be widespread.

This Apollo 16 sample displays the same characteristics of depletion of volatile elements (Rb, Cs, Pb, Cu, Ga) and increased contents of involatile elements (REE, Th, U, Zr, Hf, Nb, Ba, Sr) relative to abundances in Type 1 carbonaceous chondrites⁷, taken as approximating to the original solar nebula composition¹⁰. Eu and Sr demonstrate parallel degrees of enrichment (~ 20 times) relative to the chondritic abundances.

The strong enrichment of the involatile elements, relative to chondrites, produces element concentrations of the same order of magnitude as estimates of Earth upper crustal composition. The heavy REE (Gd-Yb), for example, are about 1.3 times the abundances in the North American shale composite sample¹¹. Other elements such as Zr, Hf, Nb, Ba have similar abundances to those in granodiorites¹².

There are wide variations in the degree of enrichment of involatile elements relative to chondritic abundances, which appear to be unrelated to volatility (Fig. 3). We note that Eu is divalent, that some Ti may be trivalent, and Cr divalent. Enrichment factors relative to chondritic abundances⁷ are given, and contour lines for equal degrees of concentration over chondrites are drawn in Fig. 3. Elements such as Mn, Ni, Co, Cr and V, entering the major Fe and Mg crystal lattice sites, are selectively retained in the lunar interior. As the size or valency of a cation departs from that of Fe^{2+} and Mg^{2+} , there is an increasing concentration of the element. We believe that this striking correlation between degree of enrichment and the important crystal chemical parameters of size and valency constitutes good evidence for processes involving crystal-liquid fractionation.

The basic assumption involved is that these selective trends are produced by fractionation within the Moon, and that there has been no selective fractionation of involatile elements between the Moon and meteorites (that is, both have similar initial REE patterns, Zr/Hf/Th/U/Nb ratios, and so on). If this assumption is correct, then these selective enrichments constitute good evidence for extensive melting and upward concentration of elements, to a degree depending on the difference between their valency and/or ionic radii from Fe^{2+} and Mg^{2+} . Similar, but more extreme, trends appear in the chemistry of the Fra Mauro Formation, sampled by the Apollo

14 mission, and in the uplands samples from the Apennine front (Apollo 15). On the basis of this geochemical evidence, we postulate an origin for the highlands by melting and fractionation of at least the outer few hundred km of the Moon.

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Relativistic Precessions of Macroscopic Objects

THE problem of extending the Thomas precession to a macroscopic object spinning about its own axis has recently been considered in connexion with a rapidly rotating disk¹. It was concluded that an arbitrary finite section of the disk would not undergo a Thomas rotation, but instead would experience "Thomas shear stresses" and that only the individual rigid units (point particles) would rotate with the Thomas precession rate. The chief aim of this communication is to point out that, if the gravitational field of the disk is not neglected, this result also holds for the analogous general relativistic precessions, and to re-examine the relativistic precessions from a more realistic microscopic point of view.

If the gravitational field of a spinning disk is not neglected it is evident from the arguments concerning the Thomas rotation of a section of the disk¹ that the above result holds for the analogous general relativistic rotations. If a small section of the disk (near the perimeter, say) was not constrained it would undergo, in addition to the Thomas rotation, two general relativistic rotations given by²

$$\Omega_1 \approx \frac{3}{2} \frac{m}{r^3} (\mathbf{r} \times \mathbf{v}) \quad (1)$$

and

$$\Omega_2 \approx -\frac{I}{r^3} \omega \quad (2)$$

In equations (1) and (2) the units are such that $c = G = 1$; m is the disk mass, $\mathbf{r}$ the radial position vector of the section, $\mathbf{v}$ the tangential velocity of the section, I the moment of inertia of the disk and ω its angular velocity. As the section is constrained

from rotating there will be (from a macroscopic point of view at least) shear stresses introduced that are completely analogous to the Thomas shear stresses. As in the case of the Thomas rotation, only the "point particles" of the disk will rotate.

I shall now consider the relativistic rotations at the point particle level. The results pertain to a macroscopic object in orbit, but they will also be applicable to a section of an object spinning about its axis. In the case of a weakly bound macroscopic object, a sphere of gas, say, in orbit in the gravitational field of a much larger mass (possibly spinning) only the individual point particles in the gas will undergo the relativistic rotations. The sphere of gas as a whole will not rotate because the individual particles are not strongly coupled to one another. But even the strong coupling of the particles is not sufficient to ensure that the entire body will rotate; the coupling forces must also be dependent on direction. For example—assuming the particles to be atoms—if an Na or Cl atom in an NaCl crystal is rotated there will be no torque exerted on neighbouring atoms and hence no torque on the crystal as a whole as the ionic bond is not dependent on direction. This is also true of the metallic bond. Classically, of course, not even an individual atom in an orbiting macroscopic object would be expected to rotate as a whole, for the principal force holding the nucleus and electron together is the Coulomb force, which does not depend on direction. It is not even certain that a nucleus (or for that matter a nucleon) will rotate relativistically as a whole, because it is a composite object. In other words, rotating a nucleon will not necessarily cause the nucleus to rotate, and rotating the nucleus will not necessarily cause the atom to rotate. (Only the electron, a point particle, is known to undergo a relativistic rotation.) Thus a necessary condition for a macroscopic object to undergo a relativistic rotation is that there be strong coupling that is dependent on direction between the composite particles at all levels. It is also apparent that if there is no strong coupling of this kind, no shear stresses will be induced. It follows, for example, that the crust of a rotating neutron star (which is a Coulomb lattice structure) will not experience relativistic shear stresses.

These results are applicable to any macroscopic object including an orbiting (or a laboratory) gyroscope². A gyroscope is merely a convenient means of defining the coordinate axis that is supposed to be rotating with respect to the fixed stars. Physically the coordinate axes may be considered as rigidly attached to the object. That the above conclusions hold for a gyroscope is easily seen by noting that all three of the relativistic rotations are independent of the angular momentum $\mathbf{s}$ of the gyroscope. Hence the behaviour of a gyroscope need only be considered in the limit $|\mathbf{s}| \rightarrow 0$, which is just the case of the macroscopic object discussed above. A metallic gyroscope will not therefore undergo the relativistic precessions. It is not clear, however, whether a gyroscope made of a material involving bonds (say) will precess. The usual result² that $\mathbf{s}$ will precess with respect to the fixed stars, whatever the microscopic structure of the gyroscope, makes the (tacit) assumption that the gyroscope is perfectly rigid and that the microscopic coupling is strongly dependent on direction.

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Experimental Comparisons of the International Pyrheliometric Scale with the Absolute Radiation Scale

THE definition of the absolute radiation scale with respect to fundamental physical concepts can be carried out by employing either a standard emitter or a standard detector of radiant flux. Standard emitters, frequently referred to as black-body sources, are chiefly employed in calibrating low level irradiance measurements. Standard detectors are more suitable for measuring the relatively high irradiance levels of solar flux.

The conventional standard emitter is a high temperature cavity radiator. Its total radiant emittance and spectral distribution can be accurately predicted from the Stefan-Boltzmann law and Planck's law, respectively, if the cavity's absolute temperature and emissivity are known. The radiation scale so defined can be transferred to a secondary detector by exposing it to the standard emitter's known flux. Irradiance measurements are then related to the absolute scale by comparing the responses of the secondary detector to the irradiance from both an unknown source and that of the standard emitter.

Standard detectors have been constructed in various forms, but they are all calorimeters in which the heating effect of an unknown irradiant flux on a detector is compared with that of an electrical current passed through a heating element placed in intimate thermal contact with the detector. An accurate knowledge of the effective absorptance of the detector for the irradiant flux, the area through which the detector is illuminated and the electrical heating power facilitates the accurate measurement of irradiant fluxes on an absolute basis.

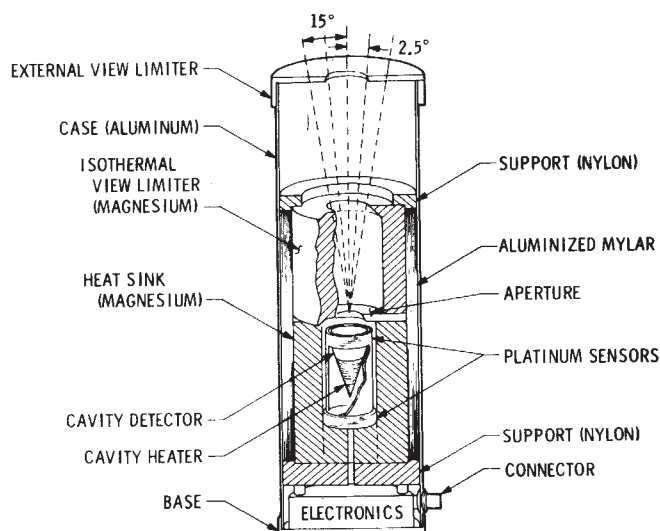


Fig. 1 JPL Active Cavity Radiometer Type III.

A series of cavity radiometers has been developed at the California Institute of Technology's Jet Propulsion Laboratory (JPL) for the accurate measurement of solar irradiance in absolute units. A first group of manually operated laboratory devices culminated in the design of the Practical Absolute Cavity Radiometer (PACRAD)¹. A second group of instruments, functionally described as the Active Cavity Radiometers, has been developed for astrophysical, meteorological and engineering applications where automatic, remote operation is required² (Fig. 1). The Active Cavity Radiometers (ACRs) and PACRADs are standard detectors of optical radiant flux. They define the absolute radiation scale through reference to an accurate knowledge of instrumental optical, mechanical and electrical parameters³. The most recently developed ACR is capable of defining the absolute radiation

scale (ARS) with an uncertainty of less than $\pm 0.5 \text{ mW cm}^{-2}$ throughout the 0 to 200 mW cm^{-2} irradiance range⁴ (Fig. 2).

A series of radiometer comparison tests has been carried out at the JPL Table Mountain Observatory, 60 mile east of Pasadena at an altitude of 2.25 km, during the period May 1968 to August 1970 (refs. 2-4). Solar irradiance measurements by instruments (Eppley Angstrom Pyrheliometers) reproducing the International Pyrheliometric Scale (IPS) have been compared with measurements made simultaneously by a number of different JPL Active Cavity Radiometers and PACRAD radiometers.

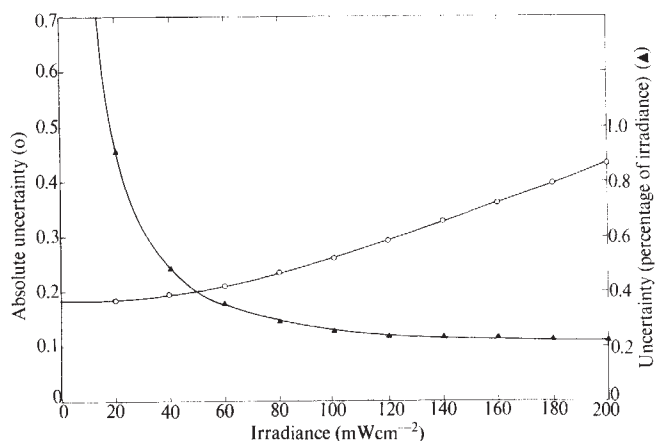


Fig. 2 Uncertainty of the Active Cavity Radiometer as a function of irradiance. Δ , % uncertainty; $\circ$, mW cm^{-2} .

The results of these tests (Table 1) demonstrate a systematic difference between the absolute radiation scale, as defined by the ACR and PACRAD measurements, and the IPS. The ACR irradiance measurements exceed those of the IPS by an average of $2.2 \pm 0.09\%$, whereas the difference between average ACR and PACRAD measurements has never exceeded 0.3% in our tests. The absolute uncertainty of irradiance measurements made by the ACR under the Table Mountain test conditions has been shown to be less than $\pm 0.5 \text{ mW cm}^{-2}$. The nominal irradiance level at this test site is 100 mW cm^{-2} , indicating that the IPS contains a systematic, absolute error of $-2.2\% \pm 0.5\%$.

Table 1 Intercomparison of JPL Active Cavity Radiometers and the International Pyrheliometric Scale

Test date (mo/day/yr)	Average value of scale difference (%)	Standard deviation of scale difference $\pm$ (%)	Absolute uncertainty of scale difference $\pm$ (%)	Weight *
5/10/68	2.0	0.13	< 0.5	355
5/11/68	2.4	0.09		370
9/23/68	2.1	0.07		612
9/24/68	2.3	0.06		4,444
9/25/68	2.1	0.04		12,500
4/23/69	2.4	0.19		138
9/22/69	2.3	0.21		91
9/23/69	2.3	0.05		12,400
8/25/70	2.1	0.25		128
Weighted averages	2.21	± 0.09	± 0.5	

* Equal to the number of independent measurement periods in each test divided by the square of the standard deviation of the scale difference.

Frohlich *et al.*⁵ report similar results from the third international comparison of pyrheliometers held at Davos, Switzerland, in September 1970. Measurements of solar irradiance on

the absolute radiation scale, defined by the JPL PACRAD and an absolute cavity radiometer developed at the US National Bureau of Standards (J. Geist, personal communication), were observed to exceed those of the Davos IPS-defining Angstrom Pyrheliometer No. 210 by $1.8 \pm 0.4\%$.

Radiometer field of view can be an important factor in solar irradiance observations made through a substantial fraction of the Earth's atmosphere. In the presence of large optical thicknesses of atmospheric aerosols, strong forward scattering (the solar aureole effect) can produce substantially different apparent irradiances for instruments with different fields of view. Ancillary experiments performed during each Table Mountain test have shown the turbidity parameter, as defined by Angstrom and Rhode⁶, to be less than 0.05. This defines, qualitatively, a relatively small aerosol optical thickness. Under these conditions, Angstrom and Rhode conclude that an equivalent circular field of view for the Angstrom is 5° – 6° . (The Angstrom's actual view limiting aperture is rectangular, subtending $4.4^\circ \times 10.6^\circ$ as seen from its detector.) The difference between the Angstrom field of view and the 5° circular ACR field of view seems to be incapable of producing a significant fraction of the 2.2% scale difference.

The Angstrom Pyrheliometer and the Abbot Water-Flow Pyrheliometer of the Smithsonian Institution are standard detectors that were developed in Europe and the United States, respectively, around the turn of the century. Both have been employed to define the absolute scale for solar irradiance measurements. Comparisons of the Angstrom and Smithsonian scale have yielded differences of up to several per cent. The absolute uncertainty of each scale has been variously estimated to be from less than one per cent to several per cent.

The International Pyrheliometric Scale is a compromise between the Angstrom Scale and the Smithsonian Scale as they were defined in 1956 (ref. 7). The IPS was created to facilitate comparison of irradiance measurements made on a worldwide basis during the International Geophysical Year. Its absolute accuracy was not of prime importance, and it is not surprising, with the advent of newer, more accurate radiometers, that it has been found to contain an absolute error of about 2%.

General knowledge of the effects of circumsolar aerosol scattering on solar irradiance measurements is incomplete. The wide range of atmospheric turbidity encountered in meteorological solar measurements encompasses a large and complex set of conditions. Although preliminary indications are that the solar aureole had no significant effect on the Table Mountain comparison tests, the investigation of the IPS-absolute scale difference should be pursued further. Precise experimental measurements of the Sun-plus-solar-aureole intensity should be made simultaneously with IPS-absolute scale solar irradiance comparisons. An accurate evaluation of the aureole effect on the scale difference could then be made by integrating the measured intensity distribution over the fields of view of the comparing radiometers.

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Visual Perception of Accelerated Nitrogen Nuclei interacting with the Human Retina

DURING Apollo 11–15, astronauts observed randomly occurring light flashes and streaks¹. Among the explanations offered is that they are caused by direct interaction of fast, heavy primary cosmic rays with the retina^{2–6}. Other suggestions include the assumption that Čerenkov light from relativistic cosmic ray particles^{7,8} or fluorescence of the lens⁹ causes the effect. Previously we demonstrated that flashes are observed in single recoil events from fast neutrons in the hundred MeV energy domain^{2,3} and by actions in the eye from fast neutrons of 25 MeV maximum kinetic energy⁶. Discrete flashes are generated by neutrons with energy ranges between 3 and 8 MeV (ref. 10), but not by neutrons of fission spectrum energies⁶. Recently, it was demonstrated that flashes and streaks are seen when single nonrelativistic helium ions (about 240 MeV) stop in or cross the retina of the human eye^{11,12}. These particles, with a linear energy transfer greater than $10 \text{ keV } \mu\text{m}^{-1}$, were seen by two subjects (T. F. B. and C. A. T.) with a 40% detection efficiency in a 4 mm diameter beam of $10 \text{ particles s}^{-1}$.

Visual phenomena have now been observed in high-energy nitrogen (7^+) beams produced at the Berkeley Bevatron¹³. Using a nitrogen beam deflected at about 266 MeV/nucleon (or 3.72 BeV kinetic energy), three scientifically trained subjects made a series of observations (E. M. McMillan, physicist; P. K. Chapman, astrophysicist; and C. A. T.). These observations confirm earlier hypotheses and argue for electronic excitation in or near the outer segments as the important mechanism.

Fig. 1 shows the general layout of experiments. Exposures were made near the focal point where horizontal and vertical dimensions were 3 mm and 20 mm respectively. A beam of 10^3 to 4×10^5 particles/pulse was detuned to decrease the particles to about 15/pulse by reducing the amplitude of the r.f. of the linear accelerator. Pulses were 1 ms duration every 4 s. The nitrogen particles of range 11.9 cm were slowed by an interposed variable water absorber¹⁴ so that they stopped in the vicinity of the eye or brain under study. The beam was collimated to 6 mm diameter by a 5 cm long brass aperture. Particles emerging from the aperture passed through a plastic scintillator approximately 3 mm thick, which counted individual particles administered to the subjects; the ionization chamber gave measurable indication only if the beam pulse had more than 10^3 , which did not occur. Elective and automatic safety controls on beam plug and Faraday cups were available. Our Human Use Committee gave a limit of 2,000 particles/person—considerably fewer than the number of flashes experienced by astronauts in a lunar flight. The eye exposure was less than 0.1 rad.

From measurements of beam quality, we know that the beam had only insignificant contamination of heavily ionizing particles appearing to be fast, heavy secondaries or accelerated $^{16}\text{O}^{8+}$ ions. Where the nitrogen particles stopped, the beam composition was greater than 60% (N^{7+}) particles, the remainder being fragmentation products of nitrogen, fast protons, and helium ions¹⁵. The heavy fragments stopped in the vicinity of N^{7+} range, whereas protons and helium ions had greater penetration. The scintillation monitor was biased so that 75% of the counts recorded by it were due to N^{7+} .

Fig. 2 is a simplified anatomy of the left eye in horizontal section showing three regions where various beam positions intercepted visual nervous structures. The accuracy of alignment was $\pm 2 \text{ mm}$ using a custom-moulded head holder.

When the beam was passed through the vitreous body or optic nerve, no streaks or flashes were seen. On passage through the posterior globe, discrete bright flashes, sometimes in clusters or interspersed with streaks, were seen as shown in Fig. 3. The colourless streaks were usually horizontal, and most were observed in the upper visual field. C. A. T. thought

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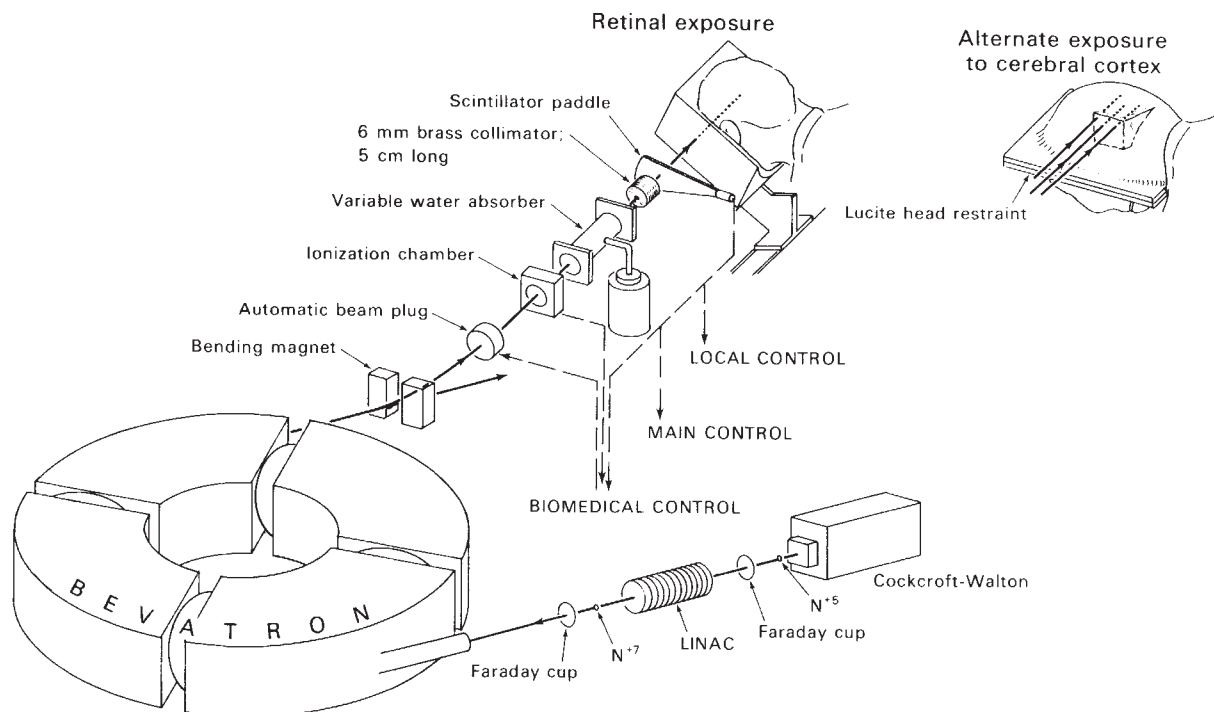


Fig. 1 Human eye and brain exposure—experimental configuration. Nitrogen ions, after final stripping, are injected into the Bevatron, accelerated to 266 MeV/nucleon, and stopped in known parts of the eye and brain.

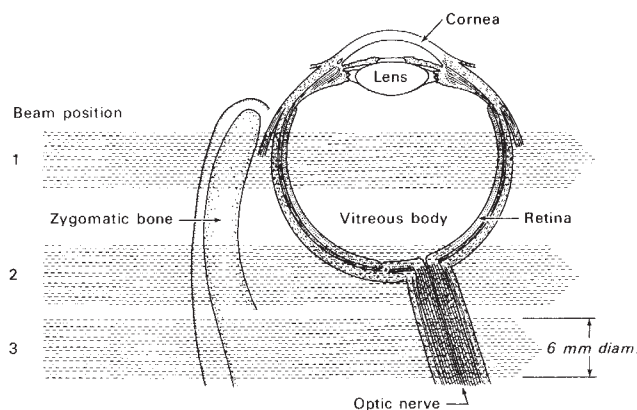


Fig. 2 Left eye horizontal section showing three nitrogen beam paths. Visual phenomena seen in middle position only.

the events observed in the nitrogen beam were brighter than events he observed in the helium ion beam¹¹. 25% of the flashes may have been due to various heavy fragments, helium ions and stopping protons.

Two observers noted a ballooning-out on the right (Fig. 3). The same observers described motion, mostly from left to right—which was the trajectory of the beam. One careful observer (E. M. M.) did not note motion or shape to streaks. Motion in streaks was also reported by C. A. T. and T. F. B. in the helium ion beam, and five subjects in the University of Washington neutron beams⁶. Particles transect the eye in about 10^{-10} s; thus the motion sense is a psychophysical phenomenon without clear explanation at present.

Throughout these experiments (and helium ion experiments) visual phenomena were seen only when the beam was positioned in the posterior portion of the eye (Fig. 2). In this position the efficiency varies with observer, and probably with atomic number, velocity, and flux density¹¹. In the nitrogen ion beam at 10 to 20 particles/pulse, observers reported stars, flashes, or streaks equivalent to 40% of particles in the beam path on entrance into the head.

From interviews with astronauts, we reconstruct the events

seen by them in space flights as follows: Stars—minute, dim, light flashes; bright flashes—like a camera photoflash 100 m distant; streaks—pencils of light varying from dim, thin lines to bright, white lines; supernovae—bright single flashes of slightly more than momentary duration surrounded by a halo less than half a degree in diameter; luminous clouds—diffuse events resembling clouds illuminated from behind. These events are depicted in Fig. 4. In the nitrogen beam, flashes and streaks were seen; E. M. M. and C. A. T. noted interrupted streaks, sometimes also termed “coincidences” or “doubles”. P. K. C. described a thick streak ending in several individual streaks. This type of event might relate to nuclear fragmentation.

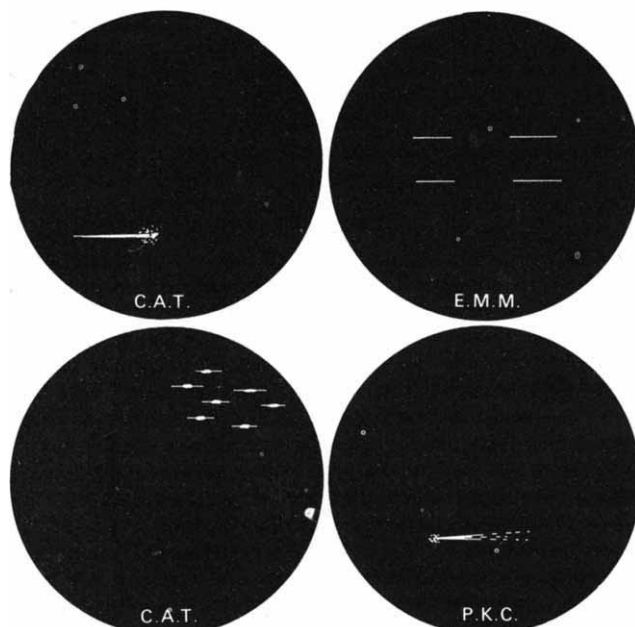


Fig. 3 Representation of visual phenomena seen by three dark-adapted observers in a nitrogen ion beam. Duration of flashes is very short without after-images.

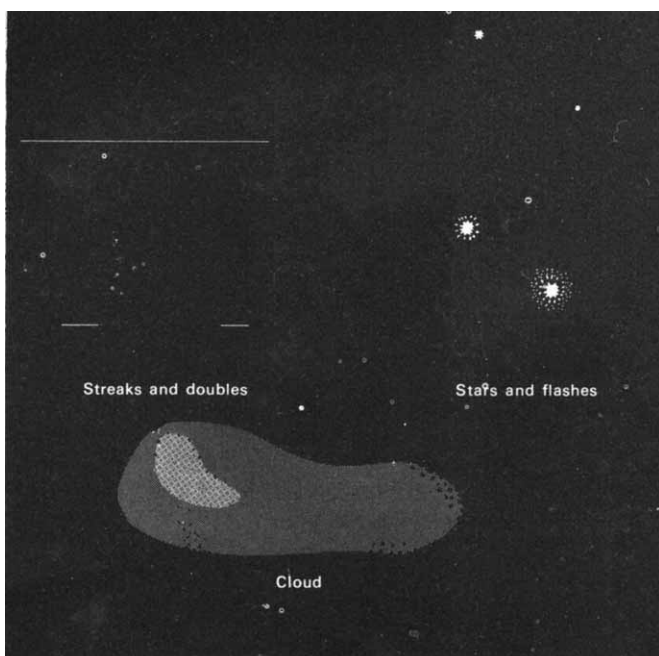


Fig. 4 Representation of visual phenomenon seen by Apollo astronauts and us, in ion beams. Cloud phenomenon is similar to X-ray, magnetic, or electrical phosphenes.

The best response was found when particles traversed skin, zygomatic bone, and soft tissue, stopping just past the centre of the retina (approximately 4.6 g cm^{-2} of residual range (in water)). When the beam was stopped in the right portion of the left retina, P. K. C. noted phenomena in the left visual field, and when stopped in the left retina, the particles appeared in the centre and right visual field, as expected.

Dependence of this phenomenon on dark adaption was shown by E. M. M. who was light adapted before entering the positioning mask. He received 6 to 10 particles in three bursts separated by a few minutes. Approximately 12 min elapsed between commencement of dark adaption and experience of flashes. He reported these flashes as dimmer than those seen when fully dark adapted. This experience corroborates that with helium ions, and is consistent with astronaut observations.

In one series, 800 particles in bursts of 3 to 40 were passed through the vitreous humour 1 cm anterior to the posterior portion of the eyeball of P. K. C.—no phenomena were seen. Fluorescence in the visual spectrum was less than 2 photons μm^{-1} when a beam of 10^4 nitrogen particles was passed through quartz chambers containing rabbit vitreous fluid, retina and lens. Fluorescence in the visual spectrum is an unlikely mechanism; however, locally deposited ultraviolet photons are still candidates, as they would not be detected by the physical experiment.

Because Penfield¹⁶ and others have evoked visual phenomena in conscious patients by electrically stimulating the visual cortex during surgery, we explored the effect of nitrogen particles on the cortex of one dark-adapted subject (C. A. T.). The 6 mm beam was aimed at the visuosensory area of the calcarine fissure, left occipital lobe. The subject wore a dark adaption mask with a water-filled plastic compartment (Fig. 1) that allowed controlled penetration of the beam into the brain when used in conjunction with the variable water absorber. A total of 900 stopping nitrogen particles were used in nine positions of various depths in the left occipital lobe. No visual phenomena were noted.

Local energy deposition (linear energy transfer) necessary for this phenomenon, as determined with helium ions, appears to be greater than $10 \text{ keV } \mu\text{m}^{-1}$ (stopping power of 10^8 eV are well localized and are different from the diffuse sensation $\text{g}^{-1} \text{ cm}^2$). Light flashes and streaks caused by single particles reported in fields of diagnostic X-ray machines or muons⁸.

Some degree of dark adaption is necessary for perception of helium and nitrogen nuclei. This suggests the outer segment of rods and cones are involved. The mechanism is dissimilar from that of electric and magnetic phosphenes, as the latter do not require dark adaption¹⁷.

Professor E. M. McMillan and Dr P. K. Chapman gave critical advice and acted as subjects. The experiments were made possible by the cooperation of Dr H. A. Grunder and the Bevatron crew. We thank J. Howard, M. C. Wales, R. E. Walton and Dr R. Thomas of the Lawrence Berkeley Laboratory for assistance. Dr Webb Haymaker aided in exposure of the cerebral occipital lobe. This work was supported by the US Atomic Energy Commission and National Aeronautics and Space Administration.

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Prediction Model for Storm Surges in the Bay of Bengal

A DEVASTATING storm struck the north-eastern coast of the Bay of Bengal near Chittagong (22.0 N, 91.5 E) on November 12–13, 1970. A meteorological analysis of the storm was recently presented by Frank and Husain¹. Storm surge data for Chittagong harbour (Fig. 1) were given to me by G. T. Bell, Royal Observatory, Hongkong.

In Fig. 1, the astronomical tide is shown by a dotted line. If this is subtracted from the gauge readings, the amplitude of the surge is 1.5 m. There is some uncertainty about the maximum amplitude of the surge because, at the time of the maximum surge, the range of the tide gauge was exceeded. I estimated the maximum surge of 1.5 m by extrapolation of the

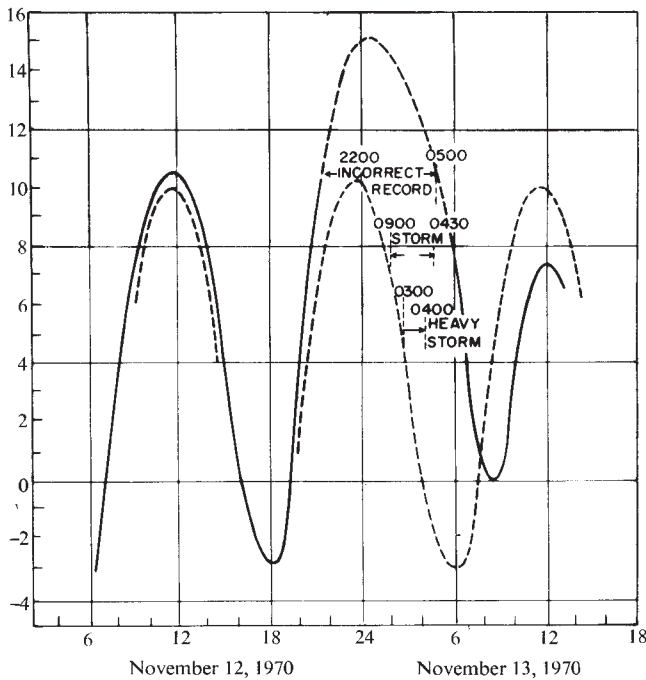


Fig. 1 Tidal curve for Chittagong harbour. Observed water levels are recorded in feet along the ordinate. Times (GMT) are indicated on the abscissa. Dashed lines represent the normal astronomical tide. The peak surge at 0100 GMT on November 13 is an extrapolated estimate.

record between 2000 GMT of November 12 and 0400 GMT of November 13. The maximum surge seems to have been reached at Chittagong at about 0100 GMT of November 13. This was nearly 2 h before the strongest winds of the storm hit the port.

Fig. 2 shows the storm track. I assumed that the distance from A to B was covered by the storm in 18 h, with a uniform speed of 20 km h⁻¹. This agrees reasonably well with the actual track and movement of the storm. Evidence from satellite pictures provides a reliable fix for the position A in Fig. 2. There is less certainty regarding the storm centre at 0300 GMT on November 13. The available winds for this

synoptic hour suggest that the position of the storm shown by B could be in error by 50 km or more.

I conducted a numerical experiment to compute the storm surge. The storm was idealized by the following profile of pressure

$$p = 1010 - 50/[1 + (r/r_0)^2] \quad (1)$$

where r is the radial distance from the storm centre, and r_0 is the radial distance at which the wind attains its maximum velocity. In the experiment r_0 was 30 km. The idealized profile assumed a central pressure of 960 mbar, and a fall of 50 mbar between the outer periphery of the storm and its centre. The maximum tangential wind generated by the idealized storm was 100 knot at a distance of 30 km from the storm centre. These values agree with synoptic evidence.

The surge height (ζ) was computed by solving the following set of three linear equations

$$U_t - fV + gh\zeta_x = -\frac{h}{\rho}p_x + \frac{1}{\rho}(F_s - F_b) \quad (2)$$

$$V_t + fU + gh\zeta_y = -\frac{h}{\rho}p_y + \frac{1}{\rho}(G_s - G_b) \quad (3)$$

$$\zeta_t + U_x + V_y = 0 \quad (4)$$

In these equations, partial derivatives are denoted by subscripts. The depth of the seabed is represented by h , ζ is the density of water, f is the Coriolis parameter and g is the acceleration due to gravity. U , V , are components of the total transport of water in rectangular cartesian coordinates. Thus

$$U = \int_{-h}^{\zeta} u dz, \quad V = \int_{-h}^{\zeta} v dz \quad (5)$$

where u , v are the eastward and northward components of motion.

I have here adopted the commonly accepted expression for wind stress (F_s , G_s)

$$F_s = k\rho'V_a/u_a, \quad G_s = k\rho'V_a/v_a \quad (6)$$

where ρ' is the density of air, V_a is the wind velocity at a height of 10 m above sea level and u_a , v_a are the easterly and northerly components of V_a . k is a non-dimensional function of the stability of the air and the wind velocity. In this experiment

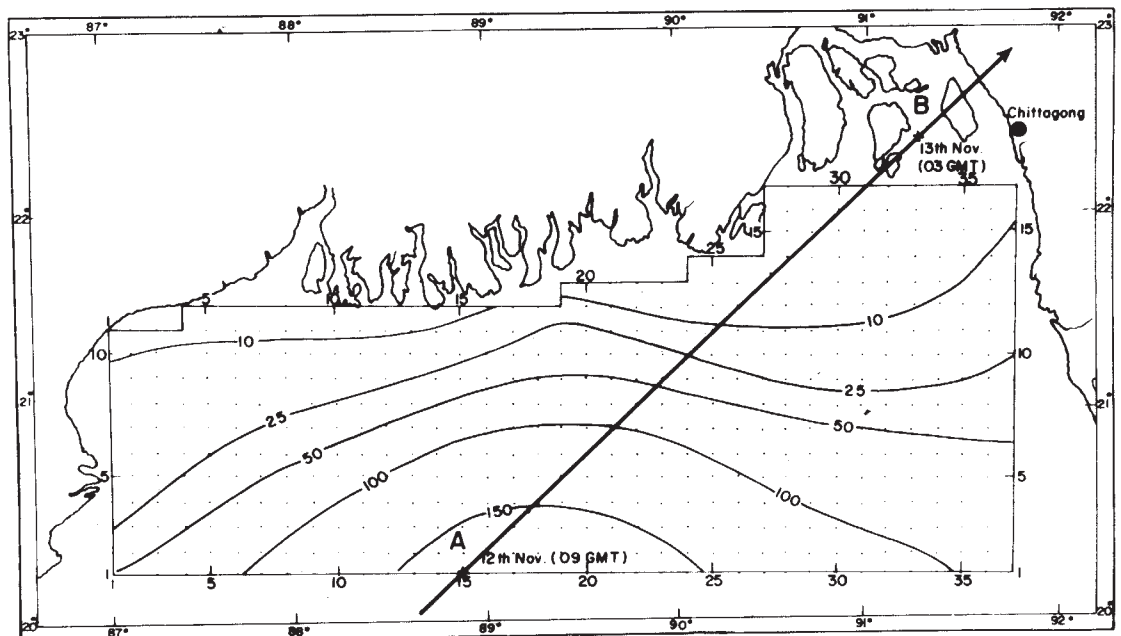


Fig. 2 Surge computation grid. Isopleths represent the depth (h) of the sea bed (m).

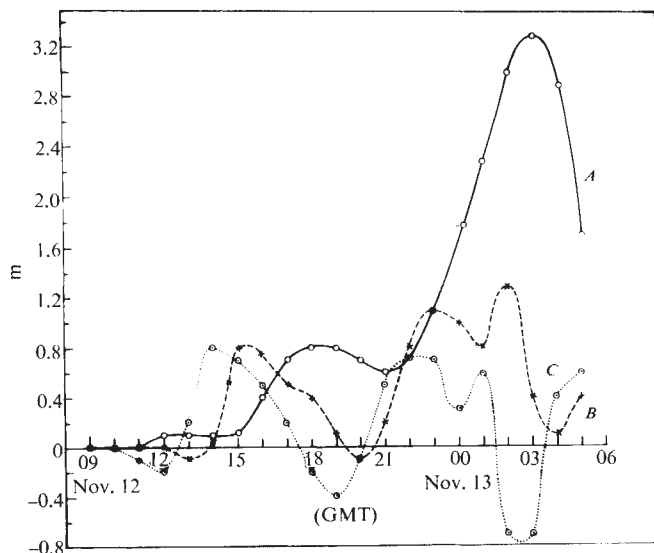


Fig. 3 Computed surge at three points (A, B and C) south-west of Chittagong. The ordinate represents surge height in metres.

k was taken to be constant. I set $k = 2.8 \times 10^{-3}$, an average value for strong winds blowing over water².

To evaluate the bottom stress components (F_b , G_b) a steady Ekman spiral was assumed over the sea bottom. For this current system, the frictional stress is proportional to the total transport of water. Consequently

$$F_b = \alpha U, \quad G_b = \alpha V \quad (7)$$

where

$$\alpha = 0.035/h^2 \text{ s}^{-1}$$

The numerical constant of the numerator of α $0.035 \text{ m}^2 \text{ s}^{-1}$ was determined empirically. The interesting feature of equations (7) is the dependence of α on the square of the depth (h).

There are uncertainties in this assumption. Ekman's spiral assumes a constant eddy stress coefficient, which is not a realistic assumption for the entire friction layer. Frictional effects are of importance only in a shallow layer near the sea bottom, and consequently it may not be correct to integrate the velocity profile in the friction layer for the entire depth of the water. It is not clear also whether the time taken to generate a boundary layer over the bottom of a shallow sea would be comparable with the growth of the surge. I propose to consider these aspects in a later study. Here, because of a large stretch of shallow sea (and small h) in the region of interest, I wish to include a simple form of bottom stress, in spite of its limitations.

The finite difference analogues of equations (2), (3) and (4) were solved over the 37×17 grid shown in Fig. 2. To satisfy boundary conditions, I precluded transport of water normal to the boundaries of the grid. The stability of the computation scheme was ensured by a unit grid of 13.8 km and a time interval of 2 min. For similar work in the past, smoothing operators have been used to achieve greater stability in numerical computations, but I found this to be unnecessary if a predictor-corrector method was used. This had the advantage of providing an estimate of the truncation error at the end of each time step. Forward time differences were used in the computations.

The growth of the surge at three points (A, B and C) south-west of the landfall is shown in Fig. 3. These points are approximately 40, 100 and 150 km to the south-west of Chittagong.

The computations reveal a maximum surge of 3.2 m at a distance of 40 km south-west of Chittagong. The model predicts a peak surge of 03.00 GMT, November 13, for the point

nearest to the landfall (A). The predicted time of arrival of the peak is within 2 h of the estimated peak surge (Fig. 1). The maximum water level also coincides with the time of heavy storm in Chittagong port. The computed amplitude is higher than that observed; but, considering the uncertainties in computing frictional stress and the ambiguity in tide gauge readings, the computed amplitudes are of the right order of magnitude.

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Deadly Surges in the Bay of Bengal: Dynamics and Storm-tide Tables

DURING the 1960s alone about 400,000 people died in the exceptionally high tides which swept in along the low lying northern coast of the Bay of Bengal under the force of tropical cyclones. Over half of these lives were lost in the single surge caused by the storm of November 1970¹. Such loss of life can be prevented only by depopulation of the area, construction of permanent defences, or by prediction of and protection against individual storms. The latter involves the identification and survey of a severe cyclone, forecast of the development and course of the storm, prediction of the sea level response, warning of danger, and protection of the survivors. We have considered the problem of sea level dynamics and prediction, and using simple mathematical models have studied the characteristics of the surge and found the sea level response to a number of model cyclones moving across the Bay along a variety of paths. Our results are summarized in a form which is handy for immediate incorporation into a warning programme.

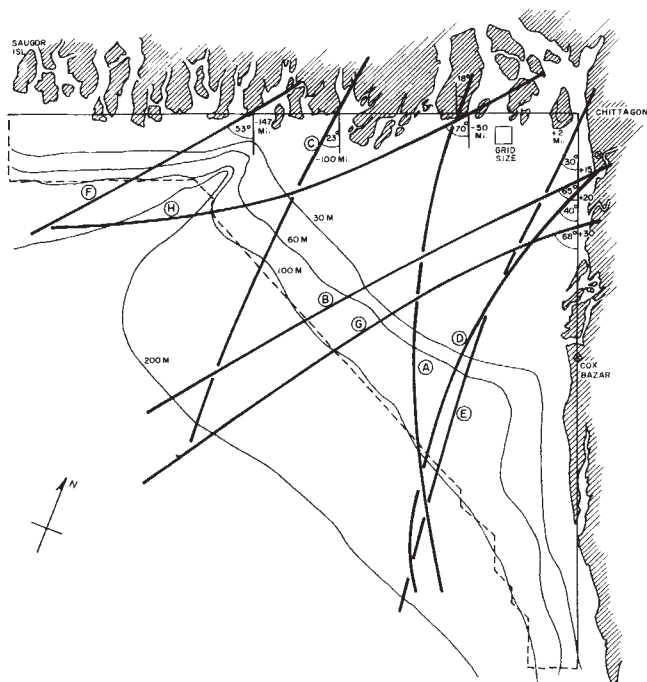


Fig. 1 The northern corner of the Bay of Bengal, geometry of the numerical model, and tracks of severe cyclones (A-H).

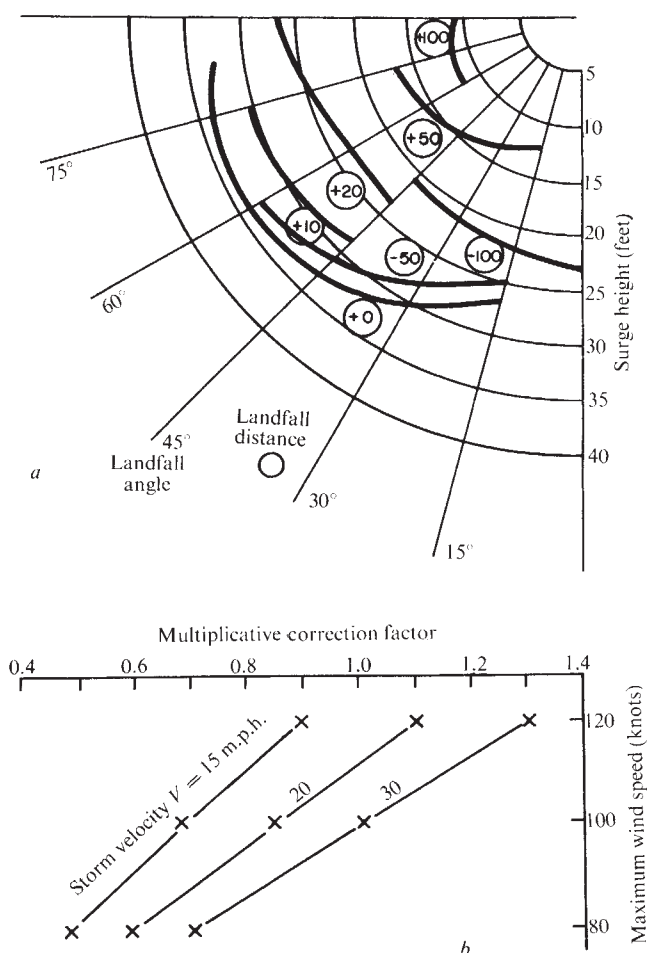


Fig. 2 *a*, Maximum surge height in response to the standard storm as a function of landfall point and track angle. *b*, Correction factor for maximum surge height as a function of maximum wind speed (W) and storm translational speed (V).

Several factors amplify surge heights in the Bay of Bengal; the large (10–18 feet) astronomical tidal range, the large expanse of shallow water overlying the broad continental shelf, and the curvature of the coastline which focuses incoming storm-induced long waves (Fig. 1). To determine the relative importance of the geometrical and geographical factors we have integrated a model storm over idealized topography and coastal configurations. If a surface wind stresses water of depth H over a distance (fetch) L , the sea level rises in approximate proportion to L/H even for the transient response of moving storms. Most of the Bay of Bengal is over 2 km deep and storm forcing becomes important only when the cyclone moves across the steep continental rise (the 100 m contour of Fig. 1) to pass over the shallow shelf. The coastline turns through a right angle at Chittagong. The maximum response

of a storm moving in to the corner of an infinite flat-bottomed ocean bounded by two straight coasts at right angles is almost double that of the same storm moving perpendicularly in to an infinite straight coastline. The maximum is composed of a direct surge contribution and a contribution reflected from the neighbouring wall. To study the effects of continental shelf configurations we used a model in which the volume of water over a shelf of finite width was held constant while the seaward slope of the shelf was varied both for a straight coastline (straight line isobaths) and a right-angle coastline (isobaths which change smoothly from right angle to semi-circular). For a given slope the maximum response in the right-angle geometry is 50% higher than in the straight geometry; in each geometry a slope of 1/25 almost doubles the ratio of response to that for a flat bottom.

The geometry of the northern corner shelf region of the Bay of Bengal and the model geometry adopted for more realistic numerical integrations are shown in Fig. 1. Long wave equations in a uniformly rotating system² are integrated over depth and linearized except for the sea-level self-interaction terms which arise from the horizontal pressure gradients and are important in very shallow regions. Bottom friction was neglected; its modelling requires careful consideration and its effect on the first surge maximum is of little practical consequence³. Fischer's⁴ simple numerical scheme was used to integrate the response to a simple model storm. The scheme and storm were calibrated by adjusting the straight coastline response curves for the height of maximum surge against distance from landfall (point at which the eye of the storm crosses the coastline) to agree (1 foot accuracy) in maximum height, half and quarter widths with Jelesnianski's⁵ more complicated storm model and more elaborate difference scheme. Our model storm was 80 miles in radius, broken down into an eye, an inner ring of strong swirl, and an outer ring of weaker swirl. The parameters which vary in each computation are the maximum swirl velocity (W), the speed of translation along the track (V) and the track itself. Computations were carried out for the region of Fig. 1 bounded by the dotted line (a nodal line of zero sea-level distortion is assumed) and the two straight coastlines, from the time the storm crosses from deep water into the region of interest until about two hours after landfall (to ensure that maximum water level has been attained).

The maximum surge height (Fig. 2*a*) occurs in response to a standard storm ($W=100$ knots, $V=30$ knots) run on straight line track as a function of track parameters, angle and landfall point. The track angle to the left of a line parallel to the Chittagong-Cox Bazar coastline is positive (Fig. 1) and the landfall distance measured in miles from Chittagong is positive towards Cox Bazar. The maximum surge occurs shortly after landfall of the storm (within two hours but usually within one hour) and very near the landfall point (within 50 miles but usually closer than 20 miles). A multiplicative factor was used to obtain actual values of maximum wind speed and storm translational motion from the values in Fig. 2*a*. These are values for storms running along 45°

Table 1 Comparison of Observed and Calculated Surges from Severe Storms during 1960–70

Storm	Date	Speed V (knots)	Maximum wind tide (feet)	Astronomical speed W (knots)	Observed sea level (feet)	Calculated sea level (feet)	No. of deaths
A	11/10/60	10	100	5.0	20	18	5,000
B	31/10/60	19	120	0.0	22	29	12,000
C	09/05/61	19	100	4.0	16	23	1,000
D	30/05/61	11	100	2.0	21	11	—
E	29/05/63	20	130	1.0	—	38	50,000
F	11/05/65	21	100	4.0	—	19	12,000
G	15/12/65	16	100	1.0	—	16	1,000
H	13/11/70	15	100	6.0	20–30	29	300,000

—, No figures available.

with landfall point zero, but can with reasonable accuracy be generally applied. As an example, an estimate of the maximum surge height caused by a storm with 90 knot winds travelling at 25 knots at an angle of 30° towards a point 100 miles west of Chittagong is $0.8 \times 22 = 18$ feet. The total sea level rise is estimated by adding to this value the predicted astronomical tide at landfall.

Figures were obtained by this method for eight severe storms which struck the area from 1960–70 resulting in over a thousand deaths (Table 1). The tracks are shown in Fig. 1. The storm and surge data were obtained from Dunn's summary⁵ and from eyewitness reports of doubtful accuracy. The recent storm H is better documented¹, but the surge may be underestimated because of the swamping of tide gauges (Das, personal communication). The data for storm E are particularly suspect. Estimations of observed surges were, however, reasonably close to calculated values. The sea level prediction technique may be improved; a worthwhile task, because the method appears to give an accurate prediction of surges. Direct prediction of a cyclone's strength and movement is difficult, but aerial reconnaissance of storms will be essential in improving forecasts.

Although protection for the low-lying coastal regions of Bangladesh and India is not at present possible, many lives could be saved by evacuation to high ground. Figs. 2a and b are a contribution to the vital warning programme.

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crystalline phases were semi-quantitatively analysed by flame emission micro-techniques, and the fluid inclusions as a whole have been examined by heating-, freezing-, and crushing-stage methods^{5,6} as well as by standard optical determinative techniques.

The inclusions within the apatites of the sövite carbonatites differ in composition from those in apatites of ijolitic intrusive complexes. The apatites in the sövites contain both aqueous gas-bearing inclusions (with crystalline daughter phases) and separate solid calcite inclusions. The crystalline daughter phases are chiefly composed of a sodium carbonate together with some calcium carbonate, and the accompanying gas phase is chiefly carbon dioxide held at a pressure of 100 to 200 bars at room temperature. The apatites in the ijolites nearby contain glasses and a variety of optically isotropic and anisotropic crystalline solids, as well as aqueous phase inclusions which differ in composition from those in the sövitic apatites.

The temperatures of homogenization recorded during heating-state experiments indicate that the minimum temperature of crystallization of the sövite is roughly 550° C. The mode of homogenization shows that, at these temperatures, carbon dioxide and water were present as a super-critical fluid, and that this fluid is capable of dissolving all the solid carbonate present—up to about 10% by volume of the inclusion. Because the inclusions are primary, they represent trapped portions of the medium in which the apatites were crystallizing. This medium constitutes a fluid carbonatite magma.

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Preliminary Evidence on the Nature and Composition of Carbonatite Magma

CARBONATITES are igneous rocks¹ but the exact nature of carbonatite magma has not been established. Silicate magmas, both extrusive and intrusive, are molten and normally carry a low-pressure gas phase. Carbonatite magmas appear also to be molten when extrusive² but there is evidence, in the form of brecciation and fenitization, that a gaseous phase plays a dominant role in carbonatite intrusions (see also ref. 3). We now report that a fluid medium capable of transporting carbonatitic material can exist, not as a molten liquid but as a gaseous and mobile supercritical fluid from which carbonatites can crystallize directly. Such a system is a strong contrast with the usual notion of an igneous magma.

A gas extraction line has been constructed for the analysis of the small volumes of gas observed in the uniform and primary fluid inclusions within crystals of apatite from carbonatites, using samples from intrusive sövitic complexes near Homa Bay in western Kenya⁴. The extracted gases were analysed by fractional freezing and by mass spectrometry. Dissolved and

BIOLOGICAL SCIENCES

Dimerization of Proflavin by the Laser Raman Temperature-Jump Method

THE effects of proflavin, 3,6-diaminoacridine, as a mutagen and as an enzyme inhibitor have been extensively studied^{1,2}. An understanding of the interaction between proflavin molecules is important in interpreting these studies. Deviations in absorbance from Beer's law indicate that proflavin aggregates at high concentrations but the extent of aggregation is uncertain³⁻⁹. NMR measurements have shown that acridine orange, 3,6-bisdimethylaminoacridine, aggregates by stacking and proflavin probably behaves similarly¹⁰. The activation parameters and interactions involved in this process are of interest because stacking interactions are believed to be responsible for the conformational stability of many biological molecules¹¹. We report here the results of a study of the kinetics of aggregation of proflavin.

Proflavin aggregation is too rapid for study with the conventional capacitor discharge temperature-jump technique. Therefore the apparatus used in this study is the laser Raman

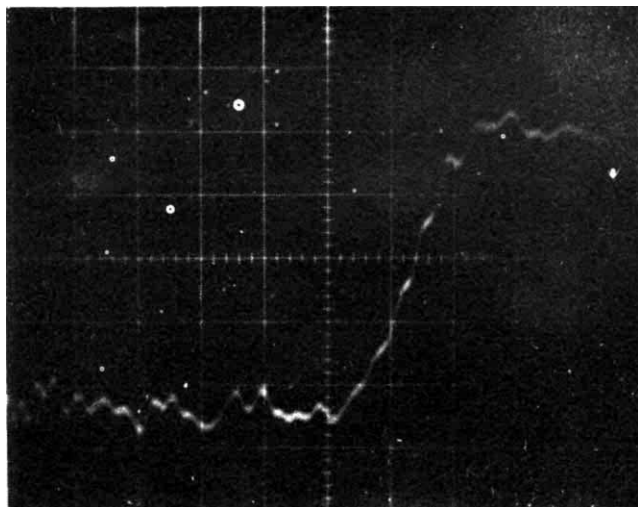


Fig. 1 Relaxation in 0.34 M $\text{Na}_4\text{Fe}(\text{CN})_6$, horizontal scale is 20 ns per division.

temperature-jump apparatus previously described¹². In this method, the stimulated Raman effect in liquid nitrogen is used to shift the output of a neodymium glass laser from 1.06 μm to 1.41 μm , where water has a strong absorption. The total heating time for this system is about 30 ns. This time was measured by using the absorbance change of 0.3 M $\text{Na}_4\text{Fe}(\text{CN})_6$ as a temperature indicator (see Fig. 1). The diffusion-controlled ion-pairing observed for this solution is expected to have a relaxation time of less than 1 ns. Thus the signal displayed effectively measures the time dependence of the cell temperature. A typical proflavin relaxation, observed at 455 nm, is shown in Fig. 2. The relaxation times for the proflavin solutions ranged from 30 to 700 ns and could be readily measured.

The large extinction coefficient of proflavin permitted the use of very thin sample cells. These were formed by placing mylar spacers with thicknesses ranging from 0.008 to 0.038 cm between two quartz windows. The corresponding temperature jumps, obtained by focusing approximately one joule at 1.41 μm into 1 cm^2 of the cell, ranged from 5.1 to 3.7° C. The cell was thermostated so that the final temperature in all cases was 25° C.

One of the hazards of optical heating is the possibility of creating two-photon effects¹³. To reduce this possibility, the

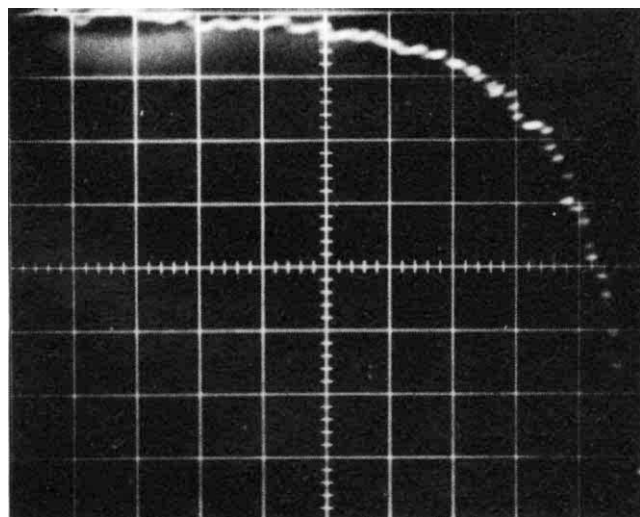


Fig. 2 Relaxation in 4.64×10^{-3} M proflavin, pH 7.8 buffer, final temperature 6° C. Horizontal scale is 200 ns per division.

unconverted laser energy at 1.06 μm was filtered out of the beam by placing a dielectric mirror between the sample cell and the liquid nitrogen dewar. This mirror reflected more than 99% of the energy at 1.06 μm , but transmitted about 80% of the energy at 1.41 μm . As an experimental check, the size of the relaxation signals was studied as a function of 1.41 μm intensity. A linear dependence was observed whereas a two-photon effect is expected to give a quadratic dependence.

Most solutions were made up in the 0.2 M KCl, 0.05 M phosphate buffer, pH 7.8, used by Shiao and Sturtevant⁵. At 25° C, a pH 4 buffer containing 0.05 M acetate and 0.2 M KCl was also used. If the observed relaxations are due to a single monomer-dimer equilibrium



then the concentration dependence of the lifetimes will have the following form:

$$\tau^{-2} = k_{-1}^2 + 8k_1k_{-1}[P]_T \quad (2)$$

where $[P]_T$ is the total proflavin dissolved. This treatment does not require prior knowledge of the equilibrium constant. The proflavin concentrations were obtained either by weight or spectrophotometrically from diluted solutions using a molar absorptivity of $3.3 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$ at 444 nm. Fig. 3 shows the plot of the data at 25° C. The points at both pH's fit a single line within experimental error. This is not unexpected since the pK 's of proflavin are 9.65 and 1.5 (ref. 14). This line corresponds to a forward rate constant of $(7.9 \pm 1.0) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ and a reverse rate constant of $(2.0 \pm 0.3) \times 10^6 \text{ s}^{-1}$ at 25° C. The resultant equilibrium constant of $395 \pm 80 \text{ M}^{-1}$ agrees well with that derived from calorimetric measurements but differs substantially from most spectrophotometric values⁶⁻⁹. The results of Shiao and Sturtevant⁵ yield an equilibrium constant of 401 M^{-1} when analysed in terms of a monomer-dimer model. Their corresponding value of ΔH is $-14.3 \text{ kcal mol}^{-1}$.

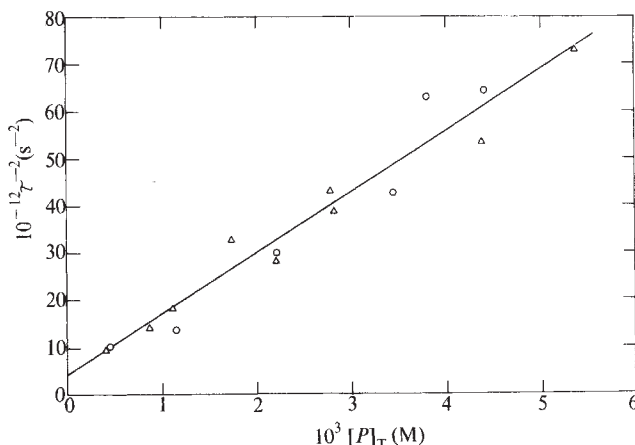


Fig. 3 Plot of square of reciprocal relaxation time versus total proflavin concentration at 25° C. $\circ$, 0.2 M KCl, 0.05 M phosphate, pH 7.8; $\triangle$, 0.2 M KCl, 0.05 M acetate, pH 4.0.

There are two ways a kinetic study can detect aggregation beyond dimerization. First, a "bending over" of the kinetic plots at high concentrations. This does not occur for proflavin as can be seen from Fig. 3. Second, the presence of more than one relaxation time. This effect has been observed in solutions of Biebrich scarlet¹⁵. No such effect was observed with proflavin. Solutions were studied at 6° C with the laser temperature-jump apparatus and at 11° C with a conventional Eigen machine. At low temperatures, the concentrations of higher aggregates should increase, but only one relaxation was observed in the nanosecond to millisecond range. Thus there

is no kinetic evidence to suggest higher aggregates. It should be noted that the lifetime measured on the Eigen machine for a 3.87×10^{-5} M solution of proflavin at pH 7.8 was equal to the heating time of the apparatus (approximately 8 μ s).

Further measurements were carried out at 6.4 and 45° C to determine activation parameters. The sum of the activation enthalpies determined from the slope of a plot of $\log(k_1 k_{-1}/T^2)$ vs. reciprocal temperature is 15.3 kcal mol⁻¹. The calorimetric value for ΔH° is -14.3 kcal mol⁻¹ (ref. 5). Using these values we calculate that $\Delta H_1^\ddagger$ and $\Delta H_{-1}^\ddagger$ are 0.5 and 14.8 kcal mol⁻¹, respectively. The former value implies that proflavin combination is diffusion controlled, a conclusion which is consistent with the value of k_1 .

The dissociation of the proflavin dimer is analogous to the melting of a double-stranded polynucleotide which results in unstacking of bases. Thermodynamic data indicate that the proflavin dimer is more stable than its nucleic acid counterpart^{5,16,17}. Thus we expect the value of k_{-1} reported here to be a lower limit for the rate of initial "unzipping" of a double-stranded polynucleotide. This is consistent with the value of 10^7 s⁻¹ calculated for this process by Eigen and Pörschke¹⁸. The rate constants for the dimerization of acridine orange have been measured by Hammes and Hubbard¹⁹. The value of k_1 is three times greater for proflavin than for acridine orange while the value of k_{-1} is a hundred times larger for proflavin. The latter difference probably reflects the hydrophilic nature of the amino groups in proflavin. One further implication of these rate constants is that it is possible to use proflavin at moderately high concentrations to detect conformational changes occurring in times greater than 1 μ s.

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Intermolecular Organization of Deoxygenated Sick Cell Haemoglobin determined by X-ray Diffraction

SICKLE cell haemoglobin (haemoglobin S), which presumably arises from a single mutation at the β -chain locus, differs from normal adult haemoglobin (haemoglobin A) by a replacement of valine for glutamic acid in the sixth position of both β -chains of the haemoglobin molecule¹. It has long been known that sickle cell anaemia erythrocytes containing deoxygenated haemoglobin S are birefringent between crossed nicol prisms^{2,3}, and that the mean plane of the porphyrin rings is approximately perpendicular to the long axis of these sickled cells². Erythrocytes containing haemoglobin A or oxygenated haemoglobin S are not birefringent. Aggregation of deoxygenated haemoglobin S, responsible for birefringence, is the basic mechanism of the sickling phenomenon. The only structural information on the aggregates has been obtained through direct observations with the electron microscope. These have revealed that deoxygenated haemoglobin S molecules in sickled cells⁴⁻⁶ and in cell-free solutions⁷ lying in parallel arrays form rod-like structures with a diameter ranging from 140 Å to 170 Å.

In this paper we report X-ray diffraction studies of deoxygenated haemoglobin S and compare these diagrams with those from oxygenated haemoglobin S. Previous X-ray diffraction studies of deoxygenated haemoglobin S in sickled erythrocytes^{8,9} showed no evidence of molecular organization greater than that existing in normal erythrocytes, but Stetson raised the question in his own studies of whether deoxygenation had been maintained⁹. Through rigorous exclusion of oxygen, and by attempting to maximize parallel orientation of rods both in cells and in haemoglobin solutions, we have obtained X-ray diffraction patterns characterizing a regularity in the aggregation of deoxygenated haemoglobin S molecules.

Suspensions of sickle cell anaemia erythrocytes, and solutions of haemoglobin S at concentrations approximating 25 to 30 g/100 ml., were deoxygenated in an atmosphere of humidified 95% N₂-5% CO₂, maintaining a pH of approximately 7.4. Cells were centrifuged at 170,000g for 1 h, a procedure which yields high proportions of elongated high density erythrocytes at the bottom of the packed cell column. These cells and the rod-like structures concentrated by centrifugation of deoxygenated haemoglobin S solutions were then introduced separately into thin-walled glass capillaries. Similarly, capillaries containing oxygenated cells and oxygenated haemoglobin solutions were also prepared. Nickel-filtered Cu radiation from a microfocus generator was collimated to give a beam of small divergence with a linear dimension of about 125 μ m at the specimen. The specimen to film distance was 45 mm to show large angle diffraction and 90 mm for the small angle reflexions. Exposures varied from 1 to 3 days. Capillaries containing sickled erythrocytes were examined under a polarizing microscope after X-ray diffraction patterns were recorded. The cells remained sickled, were birefringent, and were indistinguishable from sickled cells examined immediately after deoxygenation.

The most striking feature of the diffraction patterns of deoxygenated sickle cell anaemia erythrocytes and of the structures formed from deoxygenated haemoglobin S solutions is that the distribution of intensities is characteristic of patterns from fibres (Fig. 1). The diameter of the fibres can be inferred from the equatorial reflexions. The maxima on the equator as measured from 6 films, and averaged, are at spacings of 65 Å, 49 Å, 34 Å, and 29 Å, and the nodes are at about 54 Å, 40 Å and 31 Å. On the assumption that these maxima and the intervening nodes represent diffraction from a cylinder and are not associated with Bessel functions of zero or higher order, the measurements are consistent with diffraction from a thick-walled hollow cylinder of approximate diameter 170 Å with a central core of about 55 Å. Some observed variability in the spacings of the equatorial reflexions from preparation to

preparation represents variability in inter-fibre separation. More than 15 layer lines of periodicity 64 Å are observed (Fig. 1). Layer line spacings of all preparations examined are invariant and the distribution of intensities on the layer lines is modified only by the extent of parallel alignment of fibres. Off-meridional maxima appear on the first, second and third layers. These observations indicate that deoxygenated haemoglobin S molecules pack consistently to form the same basic structure.

Comparison of a pattern from fibres of deoxygenated haemoglobin S (Fig. 1a) with that from sickled erythrocytes (Fig. 1b) shows only small differences. The patterns from the red cells do not show as many layer lines because the background is higher and the alignment of the fibres is limited by the envelope of the cell membrane. Cells present a further difficulty in that their parallel orientation within the capillaries is poorer than that of cell-free fibres.

In contrast to the fibrous pattern of deoxygenated haemoglobin S (Figs. 1 and 2a), X-ray diagrams from oxygenated sickle cell anaemia erythrocytes (Fig. 2b) and from cell-free oxygenated haemoglobin S (Fig. 2c) do not display paracrystalline regularity. No periodicity is apparent. There is a relatively sharp intense band with centre at 62 Å and weaker bands at 32 Å, 19 Å and 13 Å, as well as a 10 Å band characteristic of diffraction from proteins. Bands at these spacings have been observed from oxygenated normal erythrocytes^{10,11}. That the patterns of oxygenated haemoglobins A and S are comparable is not surprising, as the earlier work of Perutz and co-workers¹² showed that the two crystals are isomorphous and give essentially the same distribution of intensities.

Given the dimensions of the haemoglobin molecule¹³ and of the proposed cylinder, calculations show that there are between 5 and 7 molecules on a plane perpendicular to the cylinder axis. There are thus a limited number of ways in which the haemoglobin molecules can aggregate in a regular manner to form a rod-like structure consistent with the 64 Å repeat. One possibility is that 5 to 7 apposed strands of haemoglobin molecules in register or stacked disks in register, with interparticle or disk separation of 64 Å form a fibrous structure. This model would require that all the meridional reflexions be strong. As

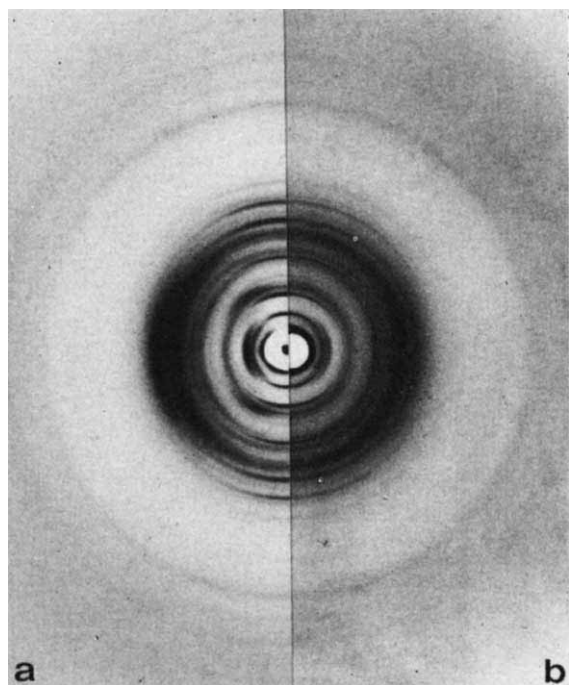


Fig. 1 X-ray diffraction patterns from deoxygenated haemoglobin S fibres (a) formed in haemoglobin solutions and (b) in sickle cell anaemia erythrocytes. Fibre axis is vertical.

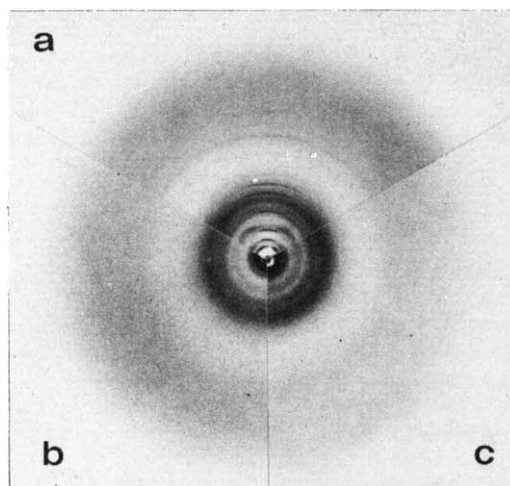


Fig. 2 X-ray diffraction patterns from (a) deoxygenated haemoglobin S fibres, (b) oxygenated sickle cell anaemia erythrocytes and (c) oxygenated haemoglobin S solution at a concentration of about 50 g/100 ml.

the fourth order is either absent or very weak, it seems unlikely that this structure is correct.

Another interpretation is that the haemoglobin molecules form into a helical array. There is a weak meridional reflexion half-way between the third and fourth layer lines of the 64 Å period, and a strong meridional reflexion at 9.8 Å, the outer limit of the diffuse band characteristic of protein scattering. These would correspond to the seventh and thirteenth layer lines of a 128 Å repeat. The presence of a meridional reflexion on the thirteenth layer line suggests that haemoglobin molecules form a simple helix of 13 molecules in two turns. Such an interpretation does not adequately explain the strong meridional reflexions on the first, second, third and fifth layers of the 64 Å periodicity.

Hence, it appears that a structure more complex than either linear apposed strands or a simple helix, as described above, gives rise to the observed diffraction patterns. Clarification will emerge from further studies at higher resolution and with preparations of fibres having better parallel orientation. Other studies in progress, including model building, are designed to give information on molecular orientation and intermolecular contacts within the fibrous structure.

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Evidence for Single Copies of Globin Genes in the Mouse Genome

It is crucial to all our ideas about the structure of eukaryotic chromosomes that we should have estimates of the numbers of copies of typical genes in the genome. Genetic evidence argues for a single copy of each gene but this is difficult to reconcile with experimental evidence that some genes, for example those specifying histones¹ and ribosomal RNA², are reiterated some hundreds or thousands of times without significant divergencies. In a previous report from this laboratory³, it was estimated that globin mRNA hybridized with an amount of DNA corresponding to 50,000 copies of globin genes. These experiments were performed in conditions of RNA excess and the hybrids were of poor quality; hence they were probably relatively non-specific and the results are readily explained in terms of hybridization of a component of the RNA with a family of repetitive sequences⁴. Similar considerations also apply to the estimate of 60,000 copies of globin genes obtained by hybridization of avian blood 10S RNA⁵. More recently, in experiments performed in conditions of DNA excess, Bishop *et al.*⁶ obtained a much lower estimate, of about five globin genes per genome, when duck 9S RNA was hybridized to excess duck DNA. These experiments have been criticized⁷ because the relationship between the rate constants for RNA-DNA and DNA-DNA hybridization reactions is uncertain and could be changed by partial degradation of RNA; moreover, a considerable fraction of the RNA remained unreacted in the presence of excess DNA even at very high C_0t values (the product of concentration of nucleic acid and incubation time expressed as mole nucleotide per litre $\times$ s).

We have used the reverse transcriptase from avian myeloblastosis virus to prepare a partial DNA copy (cDNA) of 9S RNA from mouse reticulocytes, which is known to direct mouse globin synthesis in the duck lysate⁸ or frog oocyte⁹ systems. Experiments in which cDNA is incubated in the presence of excess mouse embryo DNA show that the genes for adult globin are probably unique.

The cDNA transcribed from 9S RNA¹⁰ was fractionated on an alkaline sucrose gradient, and material ranging from 50,000 to 150,000 in molecular weight (mean at 80,000) was isolated (Fig. 1a). By buoyant density analysis the product had 40–50% G+C. Fragments of mouse-embryo DNA with a similar molecular-weight distribution (range 25,000–110,000, mean 60,000) were also prepared¹¹ (Fig. 1b).

The high molecular weight DNA (Fig. 1a) formed by incubating 9S RNA with reverse transcriptase in the presence of poly dT as primer is formed only on addition of reverse transcriptase¹⁰, 9S RNA and a small proportion of poly dT primer (unpublished results and refs. 12–14). The sequence homology between template and product was determined by hybridizing cDNA with 9S RNA (Table 1). These results show that about 5% of the cDNA anneals to itself, and that a further 85% of cDNA is complementary to 9S RNA. After ribonuclease treatment 80% of the cDNA banded in CsCl as hybrid. No hybridization of cDNA to *E. coli* RNA was observed.

To investigate the reannealing of unique DNA sequences independently of that of repetitious sequences, it is essential that the mouse DNA be fragmented to the size of the globin gene or smaller^{16,17}, as in the experiments described. More-

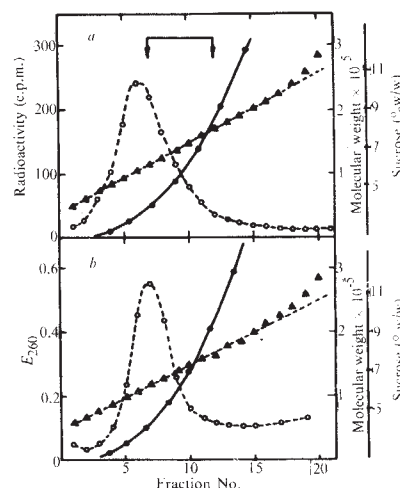


Fig. 1 Alkaline sucrose gradient sedimentation of (a) cDNA transcribed from mouse reticulocyte 9S RNA; and (b) mouse-embryo DNA fragments. *a*, 9S RNA from EDTA-treated mouse reticulocyte polysomes¹⁵ was assayed for ability to direct globin synthesis in the duck lysate system⁸. Reverse transcriptase was isolated¹⁰ from avian myeloblastosis virus. DNA complementary to 9S RNA (cDNA) was obtained by incubating 9S RNA for 90 min at 38° C with reverse transcriptase in the following mixture: 9S RNA, 5 µg/ml.; poly dT (Miles-Seravac, quoted $S_{20,w}$ value of 2.1 in 0.05 M phosphate), 1 µg/ml.; 40 µM ³H-dATP (9.5 Ci/mmol, batch 6); 40 µM ³H-TTP (11.2 Ci/mmol, batch 14); 40 µM ³H-dCTP (9.5 Ci/mmol, batch 3); 40 µM ³H-dGTP (13.4 Ci/mmol, batch 5); 20 µg/ml. actinomycin D; 100 µg/ml. catalase (type C-40, Sigma Chemical Company); 50 mM Tris, pH 8.2, 50 mM KCl, 10 mM dithiothreitol; 5 mM magnesium acetate; and one-fifth volume of reverse transcriptase in 0.15 M potassium phosphate, pH 8, containing 50% glycerol and 1 mmol dithiothreitol. Radioactive materials were obtained from the Radiochemical Centre, Amersham, and ethanol and bicarbonate removed¹⁰. Catalase was added to prevent inhibition of the reverse transcriptase by the high concentrations of radioactivity¹⁰. After incubation, the mixture, to which EDTA and *E. coli* DNA were added to give final concentrations of 2 mM and 50 µg/ml. respectively, was chromatographed on a 'Sephadex G50' column above a pad of 'Chelex 100' (BioRad Laboratories), equilibrated with 0.1 M NaCl. The excluded fraction was adjusted to contain 100 µg/ml. *E. coli* DNA and precipitated with ethanol. The precipitate was then dissolved in 1 ml. of 0.9 M NaCl, 0.1 M NaOH and layered on a linear 20 ml. 5–10% (w/w) sucrose gradient containing 0.9 M NaCl and 0.1 M NaOH. The gradient was centrifuged at 29,000 r.p.m. in an MSE 3 $\times$ 23 swing-out rotor at 20° C for 24 h; 1 ml. fractions were collected in tubes containing 10 µg of *E. coli* DNA. The molecular weight of cDNA in each fraction was determined²⁰ from *S* values calculated according to McEwen²¹. The higher molecular weight fractions (arrows) were pooled, neutralized and passed through 'Sephadex G-50'-'Chelex 100' equilibrated in distilled water. ○, Radioactivity; ▲, sucrose gradient; ●, molecular weights. *b*, About 60 mg of mouse-embryo DNA, isolated from nuclei from 16 to 18-day old mouse embryos¹¹, was incubated with DNAase I (8 ng/ml.) and fractionated on an alkaline 5–20% (w/w) sucrose gradient in an MSE titanium BXIV zonal rotor¹¹. The fragments with molecular weights similar to those of the higher molecular weight cDNA fractions were collected, neutralized and precipitated with ethanol; they were redissolved in distilled water and dialysed three times against 100 ml. of distilled water. A sample was centrifuged through an alkaline sucrose gradient as described for *a*. Symbols as in *a*.

over, interpretation of the results is simplified since the size distributions of the mouse DNA and cDNA fragments correspond closely. On the basis of the molecular weights of cDNA and mouse DNA fragments, the difference in the rates of annealing of mouse DNA or cDNA sequences of identical repetitiveness would be about 8% (ref. 18).

Fig. 2 shows the annealing of cDNA with mouse-embryo or *E. coli* DNA, determined by chromatography on hydroxyapatite. About 20% of the mouse DNA sequences reannealed at low C_0t values, after which there was progressive reannealing to a maximum of about 95% at C_0t 77,000. The C_0t_i (C_0t

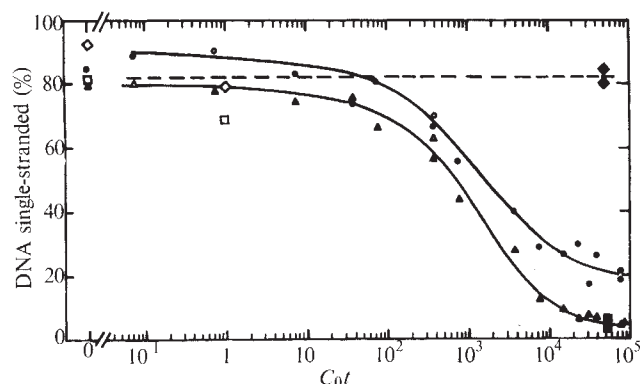


Fig. 2 Time course of reassociation of mouse-embryo DNA fragments, and of *E. coli* DNA, in the presence of ^3H -DNA transcribed from 9S RNA. A solution of cDNA (4.6×10^{-7} mg) and mouse DNA (12.3 mg) in 1.40 ml. of 0.12 M phosphate buffer, pH 6.8 (8.8 mg of mouse DNA and 3.3×10^{-7} mg of cDNA per ml.) was prepared. A mixture of *E. coli* DNA (8.3 mg/ml.) and cDNA (3.8×10^{-7} mg/ml.) in 0.12 M phosphate buffer was also prepared. For C_0t values 7.7, 77, 385 and above, 70 μl . aliquots of these solutions were sealed in capillary tubes; for C_0t values of zero, 0.077, 0.77, 38.5 and 385, 1 : 100 dilutions of these solutions (7 ml.) in 0.12 M phosphate buffer were placed in sealed test tubes. All tubes were treated twice with Repelcote, rinsed with Baycovin-treated water, and dried. All solvents and buffers were passed through 'Chelex 100' to remove heavy metal ions and treated with Baycovin, which was then destroyed. The DNA mixtures were denatured in a boiling water bath for 10 min after which they were annealed at 60° . The solutions were diluted with 0.1 M KCl, and stored at -20° until they were fractionated on hydroxyapatite (Bio-Rad 'Biogel HTP', Batch No. 7892) equilibrated with 0.03 M phosphate at 60° . About 2 ml. packed volume of hydroxyapatite was used per sample containing 0.6–0.7 mg of DNA. The column was eluted with 0.03 M phosphate buffer to remove non-retained material, then with 0.12 M phosphate buffer to elute single-stranded DNA and with 0.4 M phosphate buffer to elute double-stranded DNA. Open symbols represent the results obtained with dilute solutions, closed symbols those with concentrated solutions. The percentage of radioactivity in single-stranded DNA is shown by $\circ$, $\bullet$ (cDNA–mouse DNA) and $\diamond$, $\blacklozenge$ (cDNA–*E. coli* DNA); that of absorbance in single-stranded DNA by $\triangle$, $\blacktriangle$ (cDNA–mouse DNA) and $\square$, $\blacksquare$ (cDNA–*E. coli* DNA).

value for half-annealing) of the unique DNA sequences is 1.4×10^3 . There was no significant breakdown of the mouse DNA fragments, as indicated by binding to hydroxyapatite in 0.03 M phosphate. About 10–20% of the cDNA annealed at very low C_0t values in the presence of either *E. coli* or mouse DNA; this cannot be interpreted in terms of annealing of cDNA to repetitive DNA sequences. It possibly represents non-specific binding of a minor fraction of cDNA to either hydroxyapatite or DNA. Alternatively, a minor fraction of cDNA may possess hairpin loops which would reassociate extremely rapidly.

Table 1 Hybridization of cDNA to 9S RNA

Addition	% Radioactivity bound to hydroxyapatite	
	Double-stranded	Single-stranded
—	4	96
<i>E. coli</i> RNA (1 mg/ml.)	6	94
9S RNA (5 $\mu\text{g}/\text{ml}$.)	89	11
9S RNA (2.5 $\mu\text{g}/\text{ml}$.) + <i>E. coli</i> RNA (1 mg/ml.)	85	15

cDNA was prepared as described in Fig. 1a, except that the concentrations of deoxyribonucleoside triphosphates were: dATP, dCTP, dGTP: 500 μM ; ^3H -dTTP (11.2 Ci/mmol), 40 μM . Hybridizations were performed for 48 h at 42°C in 10 μl . aliquots in capillaries containing 1,000 c.p.m. of cDNA (about 0.015 $\mu\text{g}/\text{ml}$.), 9S RNA and *E. coli* RNA (where indicated) dissolved in 0.6 M sodium phosphate, pH 6.8, containing 50% formamide. Hybridization mixtures were analysed on hydroxyapatite as in Fig. 2. In all cases, about 95% of the radioactivity was retained by hydroxyapatite.

Initially, more than 90% of the radioactivity present in cDNA was retained on hydroxyapatite. After incubation for 4 weeks (to reach C_0t 77,000) this decreased to about 60%. Of the unretained radioactivity 80% was volatile; hence this loss of radioactivity represents tritium exchange with water rather than instability of the cDNA.

The annealing of 70% of the cDNA in the presence of mouse DNA appears to follow second-order kinetics with a $C_0t_{1/2}$ of about 1.6×10^3 , adjusted to 1.5×10^3 after correcting for the slight difference in size of mouse DNA and cDNA fragments¹⁸. There was no such annealing of cDNA in the presence of *E. coli* DNA. The correspondence between the $C_0t_{1/2}$ of the most slowly reannealing ("unique") mouse DNA fragments (1.4×10^3) and that of cDNA in the presence of mouse DNA (1.5×10^3) indicates that the number of copies of DNA sequences in the mouse genome complementary to cDNA is not detectably different from unity.

About 20% (estimated range 15–25%) of the cDNA failed to anneal with mouse-embryo DNA at a C_0t value of 77,000 (Fig. 2). Assuming that this unannealed material represents excess cDNA sequences above the number of complementary sequences present in mouse-embryo DNA, this evidence gives an independent estimate of the reiteration frequency of the globin gene. In this experiment, 4.6×10^{-7} mg of cDNA was reacted with 12.3 mg of mouse DNA. Because 20% of the cDNA was effectively annealed at low C_0t values, only 3.7×10^{-7} mg of the cDNA was available for annealing with mouse DNA at high C_0t values. Therefore, the ratio of cDNA (Y) to DNA sequences in the mouse genome complementary to cDNA (X) can be calculated from the proportions of cDNA unannealed at C_0t zero (a) and at C_0t 77,000 (b) when the reaction is virtually complete. Then $X/Y = a-b/b$. Thus when the amount of cDNA unreacted at high C_0t values is 25 to 15%, the value for X/Y is 2.2 to 4.3. Therefore, the proportion of total mouse DNA which anneals to the cDNA is

$$\frac{3.7 \times 10^{-4}}{12.3 \times 10^3} \times (2.2 \text{ to } 4.3); \text{ that is } (0.65 \text{ to } 1.3) \times 10^{-7}$$

If the double-stranded molecular weight of the haploid mouse genome is 1.8×10^{12} (5.5×10^9 nucleotides), it follows that the amount of DNA per mouse genome which hybridizes with cDNA is 117,000–234,000 (360 to 720 nucleotides). Mouse globin mRNA has a molecular weight of 170,000 (ref. 15) (about 500 nucleotides). Hence, cDNA could be complementary to 0.7 to 1.4 copies of messenger RNA specifying α or β chains. The most likely reasons for this are either random copying of one, but not both, α and β mRNAs; or non-random copying of about half of both mRNAs. A fundamentally different interpretation of these observations would be required if the fraction of the cDNA unreacted at high C_0t values represented material which cannot anneal to mouse DNA. This would lead to a higher estimate of the fraction of "unique" mouse DNA complementary to cDNA and would have to be explained on the basis of cDNA containing transcripts of several RNA species present in the 9S RNA, each of which anneals independently to separate unique sequences in the mouse DNA.

All our interpretations are based on the assumption that the reverse transcriptase produces a faithful copy of the template. Significant mismatching would affect rates of annealing of cDNA¹⁹. Provided that cDNA represents a faithful copy of at least part of mRNA specifying globin, the kinetic results show unequivocally that the adult globin genes are located in the unique fraction of mouse DNA; they also imply that cDNA does not anneal to foetal globin genes. Conclusions based on the unreacted fraction of cDNA are, however, open to a range of interpretations which can be narrowed down only by further experiments.

When our findings and those of Bishop *et al.*⁶ are compared with "RNA excess" experiments^{3–5} which conclude that globin mRNA is complementary to 50,000 sequences of the

size of a globin gene, the most likely model which emerges is that each globin mRNA is transcribed from a single locus in the genome part of which (presumably the coding portion) is unique and part of which is related to many other loci.

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Effects of Different *Endogone* Strains on the Growth of *Paspalum notatum*

IN soils containing little available phosphate mycorrhizal plants often grow much better than non-mycorrhizal ones because they can absorb more phosphate from the soil¹⁻⁴. In many tropical soils, such as the "campos cerrados" soils covering large areas of Brazil, shortage of available phosphate is a main factor limiting plant growth and there is no response to nitrogen until the phosphate deficiency is relieved⁵. In such soils inoculation with a mycorrhizal fungus may be beneficial, even though most soils naturally contain some fungi that form vesicular-arbuscular (VA) mycorrhiza. The indigenous mycorrhizal fungi can be killed by irradiation and VA mycorrhiza can then be re-established by inoculation with species of *Endogone*. Several different strains exist and effects of four

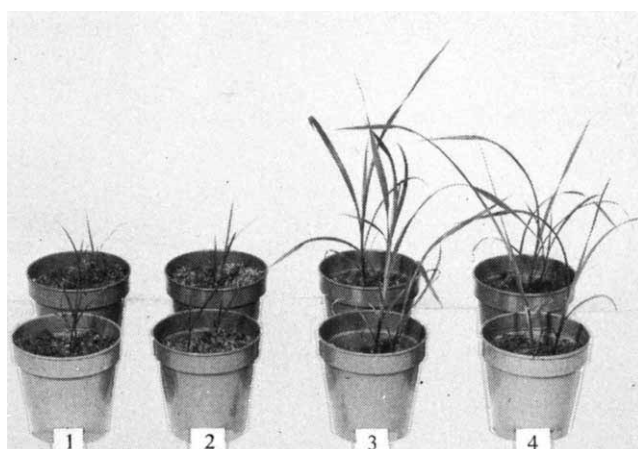


Fig. 1 Effect of phosphate (P) and nitrogen (N) on the growth of *Paspalum notatum* seedlings in soil B. 1, Control; 2, N added; 3, P added; 4, N+P added.

strains on the growth of the tropical grass *Paspalum notatum* var. Batatai were compared in two Brazilian soils.

Phosphorus and nitrogen contents of the two soils are given in Table 1 and the plant response to the addition of phosphorus (P), nitrogen (N) and to both (N+P) in one soil is shown in Fig. 1. Responses in the other soil were similar. Nitrogen as NH_4NO_3 (17 mg/pot) and phosphorus as K_2HPO_4 (13 mg/pot) were applied in solution to the soil, previously sterilized by gamma irradiation (0.8 Mrad) and diluted with an equal volume of sand containing neither P nor N.

To test the effect of VA mycorrhiza, irradiated soil was inoculated with three purified strains of *Endogone*, E_3^7 , honey-coloured⁸ and laminate⁸. The effect of an indigenous mycorrhizal fungus, probably also a species of *Endogone*, occurring in *P. notatum* from another part of Brazil, was also tested, using mycorrhizal roots as inoculum. All test plants were grown from seed sterilized in concentrated H_2SO_4 and germinated in sterile sand. Controls were of two kinds: seedlings grown in the unsterile soil (these were expected to become infected with the indigenous mycorrhizal fungi present in that soil) and seedlings grown in irradiated soil to which twice-filtered leachings from the unsterile soil had been added. Such leachings contain the indigenous bacteria but no mycorrhizal fungi. Because some *Endogone* strains do not grow well in very acid soils, 0.15 g of lime/100 g soil was added to half the pots of soil A, and 0.25 g/100 g soil to soil B. All the plants were watered with de-ionized water and no further nutrients were supplied during their growth.

All seedlings grew equally well during the first four weeks, but then control plants started to decline while mycorrhizal plants made vigorous new growth. Table 2 gives the mean dry weight of shoots of eleven-week-old seedlings and Fig. 2 shows the plants in soil B shortly before harvest. In both soils, control plants, whether grown in unsterile soil or in irradiated soil with leachings, remained very small and were little improved by adding lime. Some infection by indigenous

Table 1 Nitrogen and Phosphate Content and pH of Two Brazilian "Cerrado" Soils

Soil	0.01 M CaCl_2 -soluble P* ($\mu\text{mol l}^{-1}$)	0.5 M NaHCO_3 -soluble P† (mg/1,000 g soil)	Total P (mg/1,000 g soil)	Total nitrogen (%)	pH
A	0.44	1.68	412	0.17	4.5
B	0.37	2.94	328	0.16	5.2

* See ref. 10.

† See ref. 11.

CaCl_2 -soluble P and NaHCO_3 -soluble P are measures of two (possibly to some extent overlapping) fractions of total soil phosphorus readily available to plants.

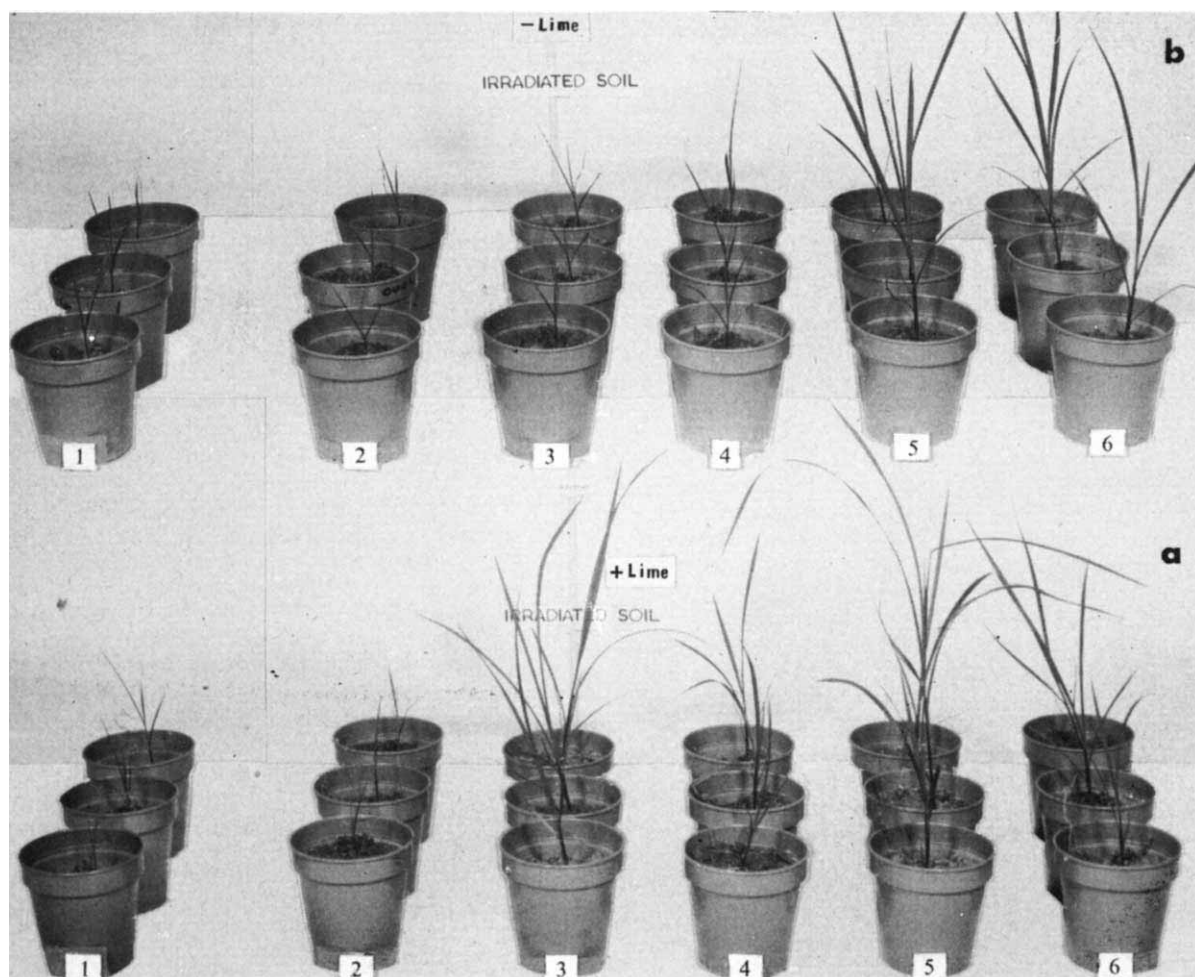


Fig. 2 Effect of inoculation with different mycorrhizal strains of *Endogone* on the growth of eleven-week-old seedlings of *Paspalum notatum* in soil B with (a) and without (b) lime. 1, Unsterilized soil; 2, leachings added; 3, mycorrhizal root inoculum; 4, laminate strain; 5, E_3 strain; 6, honey-coloured strain.

mycorrhizal fungi occurred in the unsterile soils, but only slightly improved growth. In general, control plants grew slightly better in soil B, possibly reflecting its greater NaHCO_3 -soluble P content. Inoculation with the four strains of mycorrhizal fungi improved growth almost to the extent of added phosphate; up to eleven-fold in soil B with lime and up to five-fold without. In soil A the improvements in the unlimed soil were much smaller (only about two-fold), although the final pH of the two unlimed soils differed by only 0.1 unit.

The different strains of mycorrhizal fungi differed in their effects; the laminate spore type was always poorest and E_3

most consistently good. The beneficial effect of the root inoculum was greatly increased at pH 5.8 (in soil B), and was possibly directly pH dependent, whereas the honey-coloured spore inoculum was best at pH 4.8 in soil B and was in both soils a good inoculum for the unlimed soil. Benefit from a particular strain was not always correlated with the extent of root infection caused by it.

That some mycorrhizal strains of *Endogone* can be more beneficial to their host than others confirms recent results with peach seedlings grown in zinc-deficient soils in California⁹ and with onions and grasses grown in different soils from Great Britain.

Table 2 Dry Weight of Shoots and Mycorrhizal Status of *Paspalum notatum* Seedlings

Soil	Inoculum	Shoot dry wt (mg) and mycorrhizal status (ms)							
		Soil A				Soil B			
		+ Lime (pH 5.0)	ms	- Lime (pH 4.7)	ms	+ Lime (pH 5.8)	ms	- Lime (pH 4.8)	ms
Irradiated	E_3	40 $\pm$ 6	m	12 $\pm$ 1	m	115 $\pm$ 21	m	58 $\pm$ 9	m
Irradiated	Honey-coloured	34 $\pm$ 1	m	10 $\pm$ 2	m	41 $\pm$ 8	m	65 $\pm$ 1	m
Irradiated	Root inoculum*	27 $\pm$ 4	m	6 $\pm$ 2	m	79 $\pm$ 11	m	14 $\pm$ 2	m
Irradiated	Laminate	14 $\pm$ 4	s	4 $\pm$ 1	—	33 $\pm$ 7	m	16 $\pm$ 2	m
Irradiated	Leachings	7†	—	5 $\pm$ 1	—	10 $\pm$ 2	—	11 $\pm$ 1	—
Unsterilized	None	10 $\pm$ 1	—	8 $\pm$ 2	s	14 $\pm$ 1	s	8 $\pm$ 1	s

Soil A, mean of two replicates; soil B, mean of three replicates.

pH of the soil was determined at the end of the experiment.

* Mycorrhizal roots of *P. notatum* from another region.

† One plant only.

m, All plants mycorrhizal; s, some plants mycorrhizal; —, no plant mycorrhizal.

The seedlings were grown in two Brazilian soils inoculated with four different vesicular-arbuscular mycorrhizal fungi.

In these soils also strain performance was influenced considerably by soil and liming. It is not known whether the effects of lime are due to pH changes directly affecting fungal growth or phosphorus availability, or whether there is also an effect of calcium. As plant growth can be greatly improved by addition of more efficient strains of mycorrhizal fungi, the possibility of increasing yields by introducing such strains should now be tested under field conditions. Inoculation could be useful where fertilizer transport is prohibitive, but perhaps even more in ensuring a better utilization of applied phosphate, which rapidly becomes unavailable to plants in many soils. In pot experiments⁶ selected *Endogone* strains have been successfully established in natural unsterilized soils in competition with the indigenous microorganisms.

In "campos cerrados" soils considerable improvements could also be expected in growth of Pangola grass (*Digitaria procumbens*) and in alfalfa (*Medicago sativa*), two economically important plants that, according to McClung *et al.*⁵, are even more responsive to phosphate.

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Physiology of Brood Incubation in the Bumblebee Queen, *Bombus vosnesenskii*

ONE of the parameters affecting the rate of growth and reproduction of poikilothermic organisms is temperature. In social insects such as bumblebees¹⁻³, which must build up their colonies rapidly to complete the cycle within a single season, the maintenance of a high nest temperature would permit the more rapid development of the poikilothermic eggs, larvae and pupae. Although heat production by bumblebees in their nests⁴ has been observed since the last century, little is known about nest temperature regulation in the initial stages of colony founding⁵⁻⁷. The queen initiating the colony in the spring perches on her brood clump containing the eggs which develop into the first set of workers¹⁻⁶. I report here on the temperatures of the brood clump, the attending queen, and her thermoregulatory physiology.

Bombus vosnesenskii Radowskowsky queens were obtained near Berkeley, California, in January while they were foraging from manzanita (*Arctostaphylos* sp.). The bees were maintained in the laboratory where they were provided with ample sucrose solution. The queens utilized pollen clumps (on the floor of the cage or in nest boxes) as oviposition and "incubation" sites. Temperatures of such "brood" clumps, and control clumps without a bee, were measured with 40 gauge cc thermocouples implanted in the approximate centre. Temperatures were recorded with a Honeywell multichannel potentiometric recorder at 12 s intervals or less for 24 h or more. Body temperatures of bees were similarly recorded from 46 gauge

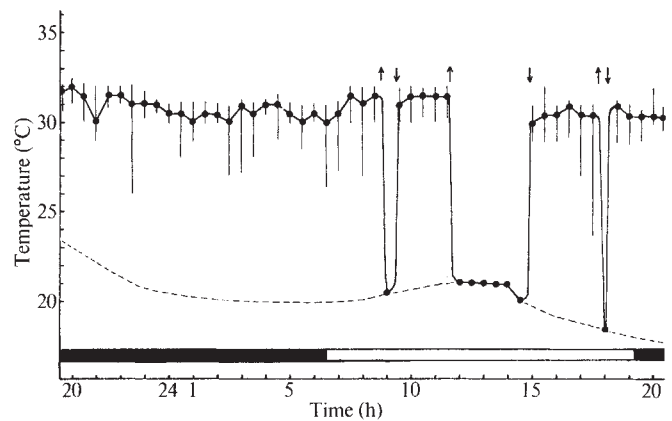


Fig. 1 Brood clump temperature (in the approximate centre) over a 24 h cycle of true solar time. Temperatures were recorded at 12 s intervals. The points represented for each 30 min give the temperature judged to be average for that duration. The maximum and minimum recorded temperatures for these periods are represented by thin vertical lines. The dashed line indicates the temperature of a control clump of pollen without a bee on it, which reflects ambient temperature. Arrows indicate when the queen went on to the brood, and when she left it, but durations less than 15 min off the brood are not indicated. The weight of the bee was 0.62 g and the weight of the brood clump was 1.21 g. ●, Brood; ---, control.

cc thermocouples implanted in both thorax and abdomen.

The temperature of the brood clump (usually measured without nest insulation) on which a queen was perched was always considerably higher than that of the control clump. The times at which a bee attended her clump varied, however. A bee would often leave her brood clump for short durations during the day, but usually remained on it continuously at night. One queen maintained her brood clump containing small larvae near 30°–32° C at ambient temperatures (T_A) of 18°–24° C (Fig. 1), and when T_A was reduced to 3° C (by immersion of the cage into ice) a maximum difference of 21° C between the brood clump and the control was observed for up to an hour before brooding was terminated at these lowest temperatures. When T_A was increased to 30° C, however, the difference in temperature between brood and control clump (with the bee still perched on the brood) declined to about 2° C. These data indicate that the brood clump is incubated, and that its temperature is to some extent independent of ambient temperature.

Brood incubation is energetically expensive. The food intake (at 20°–23° C) of non-incubating queens, which enter torpor at night⁸, ranged from 0.30 to 0.38 ml. 50% sucrose solution per day. In contrast, incubating queens, which may maintain their thoracic temperature (T_{Th}) near 35°–38° C nearly continuously during the daytime as well as at night⁸, consumed at least three times as much sucrose.

Heat of sufficient quantity to raise T_{Th} is produced only during flight, and during "warm-up" when the flight muscles in the thorax are activated by typically synchronous bursts of nervous impulses⁹. Increases of abdominal temperature (T_{Ab}) above T_{Th} were not observed, and all increases of T_{Ab} above T_A were preceded by heat production in the thorax. Increases of T_{Ab} were frequently accompanied by simultaneous decrease of T_{Th} (Fig. 2). It can be inferred that temperature increases in the abdomen (which contains negligible muscle mass) result from heat derived from the thorax. During pre-flight warm-up (Fig. 2), flight (Table 1), and intermittent activity¹⁰, the difference in temperature between thorax and abdomen is usually pronounced. The mean T_{Ab} of queens during incubation, however, was only 1.6° C from the mean T_{Th} , and this T_{Ab} was significantly higher ($P < 0.01$) than that observed in non-incubating queens with similar T_{Th} (Table 1). On the basis of mean temperatures and weights of thorax and abdomen (36.9° C, 0.23 g; 35.3° C, 0.34 g) it can be shown that the

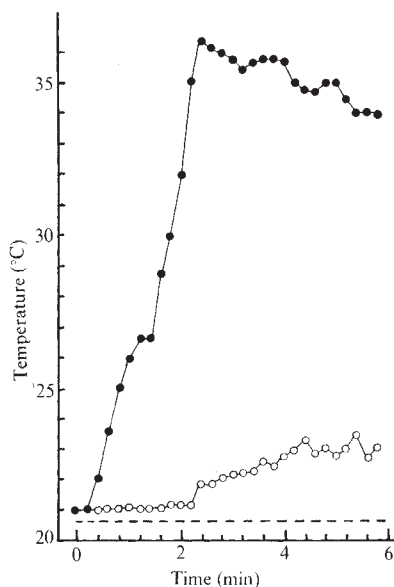


Fig. 2 Thoracic (●) and abdominal temperature (○) recorded from a queen during warm-up and subsequent on-off flight.

abdomen, during incubation, contains approximately 30% more heat at any one time than the thorax. In addition, the abdomen of incubating queens (but not of non-incubating queens) is in direct contact with the substrate and should lose heat continuously by conduction. The passive conduction of heat from thorax to abdomen, however, is slight; when the thorax of a dead bee is electrically heated to over 40° C (by means of an implanted resistor) the increase in temperature of the freely suspended abdomen is no more than 2° C. The above data indicate that: (1) the abdomen (in dead bees) is physically isolated from the thorax with regard to heat flow from the thorax, (2) non-incubating queens may sequester heat in the thorax, and/or (3) incubating queens actively transport heat from the thorax to the abdomen.

Table 1 Thoracic (T_{Th}) and Abdominal Temperature (T_{Ab}) of Flying Queens, Stationary Queens (with Rapid Abdominal Respiratory Movements) and Incubating Queens

	T_{Th}	T_{Ab}	$T_{Th}-T_{Ab}$
Flying	39.20 ± 1.36 (5)	29.30 ± 2.71 (5)	9.90 ± 2.08 (5)
Stationary	37.10 ± 1.67 (5)	29.50 ± 1.67 (5)	7.60 ± 0.97 (5)
Incubating	36.86 ± 0.68 (7)	35.29 ± 0.53 (7)	1.56 ± 0.59 (7)

Ambient temperature was 21–23° C.

The numbers indicate: mean $\pm$ 2 s.e. (the number of measurements from different queens). The temperatures given above were obtained by grasping bees and quickly inserting a rigid sharpened 30 gauge thermocouple into the body. Temperatures were read in 5 s or less, and each bee was discarded after T_{Th} and T_{Ab} were recorded. (Continuous records of T_{Th} and T_{Ab} during incubation are not reported because the bees were unwilling to incubate with thermocouple lead dangling from thorax or abdomen.)

During incubation the queen straddles the brood clump with her legs, extends her abdomen, and flexes it while applying it to the brood clump. (The ventrally protruding coxae on the thorax prevent a smooth and continuous contact with the brood clump at the thorax.) The major area of contact between the bee and the brood clump is the ventral surface of the abdomen, which is the only relatively large area of the bee which is nearly devoid of pile. The thorax and the dorsum of the abdomen, on the other hand, are covered with a dense layer of pile which nearly halves the rate of heat loss¹¹.

Freshly killed queens were fixed onto their brood clump in the incubation posture with thread and a small amount of

honey (to assure contact). A thermode, implanted either in the thorax or in the abdomen, was heated electrically to achieve the desired heat input, while thermocouples in various portions of the bee and the brood were used to record temperatures simultaneously. Little temperature increase of the brood was noted when T_{Th} was maintained at 43° C (Fig. 3). When the abdomen was given the same heat input with the thermode as the thorax, however, the temperature of the brood increased nearly in parallel with that of the abdomen (Fig. 3).

I conclude that the bumblebee queen, *B. vosnesenskii*, incubates her initial brood cluster. Morphology, behaviour, body temperatures of live bees and heating experiments with dead bees indicate that the brood is heated primarily through the abdomen even though the heat generating mechanism (the flight motor) is located exclusively in the thorax. The queen apparently controls the transfer of heat from thorax to abdomen, but stationary bumblebees can also cease the production of heat⁸ and presumably vary the rate of heat production.

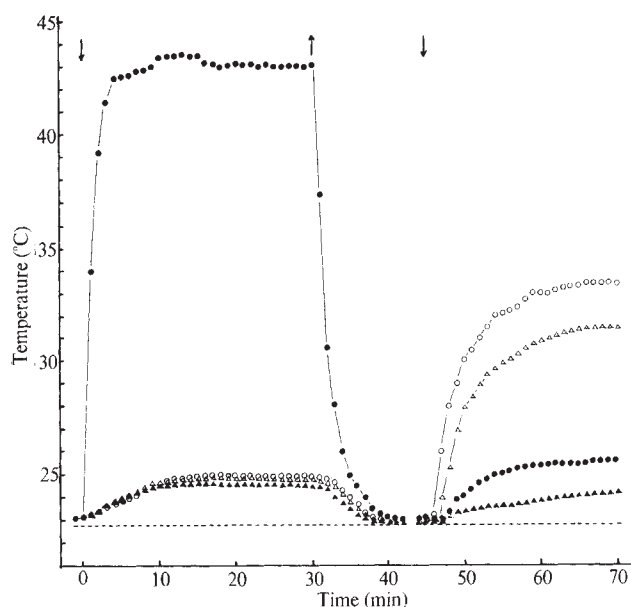


Fig. 3 Temperature changes in a bee-brood incubation system using a freshly killed *B. vosnesenskii* queen. The bee was heated first through the thorax (●). After cooling to ambient temperature (---) the thermode was implanted into the abdomen (○) and the same heat input was applied as to the thorax. Temperatures were measured inside the pollen clump ("brood") both under the thorax (▲) and under the abdomen (△). The weight of the bee was 0.70 g, and the weight of the pollen clump was 1.19 g. Position of the thermocouples was the same throughout the experiment. Arrows indicate heat-on and heat-off.

Heat transfer from the thorax to the ventrum of the abdomen (from where it is rapidly lost to the environment) has previously been observed in a large sphinx moth during free flight at $T_A > 20^\circ \text{C}$ ¹². In the moth, blood circulation, which transports heat and stabilizes T_{Th} by preventing overheating, was identified as the vehicle of heat transfer¹³. The heat generated by the flying moth, however, is an unavoidable by-product of the flight metabolism.

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Correlation of Ant Alarm Pheromone Activity with Molecular Vibration

THE alarm pheromones of certain species of ant provide extraordinarily favourable tools with which to examine the relationships between molecular characteristics and biological activity.

After the identification of 2-heptanone as the alarm pheromone of *Iridomyrmex pruinosus* (Roger)¹, a number of substances, many with structures related to 2-heptanone, were tested for pheromone activity which was estimated on a 0 to 5 scale of intensity, depending on the number of ants showing a typical alarm response². The tests were made both in the laboratory and in the field and were replicated many times. The pattern of response looked for included faster movement, attraction toward the stimulus, and occasionally attacks by one ant on another. In the absence of evidence to the contrary, a similar response can be regarded as evidence of similarity in the sensory input from the stimulus molecules.

J. E. Amoore believes that molecular shape plays an important and perhaps a dominant role in governing the biological activity of these quasi-alarm pheromones³. It is important, therefore, to see whether the biological activity of these compounds is equally compatible with the alternative hypothesis that olfactory specificity is a function of the molecular vibration pattern⁴.

Through the courtesy of Professor M. S. Blum and Dr Amoore, compounds showing varying degrees of activity on the 0–5 scale were available for examination in the far infrared range from 500 to 100 cm⁻¹. The results were evaluated by comparing the spectra of nineteen substances having activities of 5, 4, and 3 with the spectra of twenty-six substances with activity 0, setting aside as only marginally active, those with ratings of 2 and 1. Inspection of the data suggested a possible correlation of the biological activity with the following specification:

"Favourable frequencies" (any one or more likely to confer biological activity): 210–222; 325–335; 428–438; 440–449; 479–489 cm⁻¹; "adverse frequencies" (either one likely to negate pheromone activity): 177–197; 350–360 cm⁻¹.

Of the nineteen unequivocally active compounds, seventeen met this specification, whereas of the twenty-six inactive ones,

only six did so. The six inactive compounds which conformed with the specification may owe their lack of biological effect to insufficient volatility or to steric requirements affecting the probability of a quantum exchange with the receptors. Nevertheless, the coefficient of association $(17 \times 20 - 2 \times 6) / (17 \times 20 + 2 \times 6)$, is 0.93, demonstrating the close correlation that can be found between a simple pattern of vibrational bands and the biological activity. For this association χ^2 is 16.8, indicating a highly significant correlation. The two active compounds which did not fully meet the vibrational specification were 2-nonanone and 2-butyl acetate. Each had two "favourable" frequencies, but the first had an "adverse" one at 196 and the second one at 352 cm⁻¹. In view of the limited data and the uncertainty in the precise position of absorption maxima in survey-type spectra run on liquid or dissolved samples, these apparent exceptions cannot be regarded as insuperable obstacles to the theory.

The critical test of a theory is its ability to generate verifiable predictions, and especially predictions which would not be derivable from alternative or competing theories. Accordingly, available far infrared spectra were searched for compounds which met the above tentative specification and the molecular configurations of which seemed to be quite unlike that of the natural pheromone, 2-heptanone.

Nine such compounds were selected and available for testing (Table 1). It was not possible to repeat the very comprehensive laboratory and field tests which led up to the assignment of ratings on the 0–5 scale. Instead, 0.5 μ l. of the substance was drawn into a glass capillary and the tip brought to within 2 cm of quietly feeding ants and the response looked for was a general agitation, increased running about, and attacks on other ants, all manifested within 10 s of introducing the test chemical. If the agitation was especially marked and appeared within 5 s, the response was rated ++. A distinct but less marked response appearing within 10 s was rated +, and little or no response was rated –. All the compounds were assayed on five separate laboratory colonies of ants.

Table 1 shows that seven of the nine compounds which met the vibrational specification gave a distinct response, and there is an indication that the 440–449 cm⁻¹ band may not be as significant as the rest. Two compounds, isovaleric acid and triethyl amine induced additional "cleaning movements" by the ants.

These results follow other predictive successes of the vibrational hypothesis, namely, the successful prediction of wasp attractant properties⁵, the anti-attractant effect of compounds carrying "adverse frequencies"⁶, and the successful selection of compounds with a "green" type of odour⁷. A correlation of pheromone activity with the shape of 2-heptanone seems to be wholly incapable of accommodating, not to mention predicting, the alarm pheromone activity of such substances as triethyl amine, heptyl butyrate or terpineol acetate. It can, of course, be argued that the response to these compounds is not a true "alarm response", but until means are found for discriminating very subtle differences in the response pattern, similarity of response must be regarded as *prima facie* evidence of similarity of sensory input.

Table 1 Infrared Spectra and Bioassay of Putative Pheromones

Compound	Bioassay	Infrared bands						
		210–222	325–335	Favourable 428–438	440–449	479–489	Adverse 177–197	350–360
Triethylamine	++	—	328	438	—	483	—	—
Heptyl butyrate	++	217	334	428	—	479	—	—
2-Methylpentyl crotonate	++	—	333	432	—	480	—	—
4-Methyl-3-heptanone	++	215	333	438	—	—	—	—
Terpineol acetate	+	216	333	432	—	481	—	—
Isovaleric acid	+	221	328	428	—	489	—	—
d-Limonene	+	—	329	428	—	489	—	—
o-Anisil	—	—	333	—	443	483	—	—
Geranyl formate	—	—	328	438	447	—	—	—

The ability to predict is a more stringent test of a theory than the ability to correlate existing knowledge. The success of the vibrational hypothesis in both predicting and correlating lends confidence to a belief that the relationship between alarm pheromone activity and molecular vibration is indeed a valid general principle.

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Stereochemical and Vibrational Theories of Odour

IN a recent communication¹ and accompanying editorial comment², it has been asserted that Amoore's stereochemical theory of odour is validated (and the vibrational theory discredited) by a correlation coefficient of 0.90 between subjectively estimated odour similarities of a number of substances to benzaldehyde (taken as a standard), and a computer-generated scale of molecular shape resemblances. These claims can be questioned on several grounds.

The computer-generated molecular shape factor, which is derived from three orthogonal silhouettes, is used to represent the whole stereochemical aspect of the molecule by a single 3- or 4-digit number, it must surely be inappropriate to reduce anything as intricate and variable as a molecular shape to a single number. In fact, Amoore's procedure would assign exactly the same numerical parameter to very many different three-dimensional profiles³. The richness and variety of olfactory sensations calls for a degree of stimulus specificity that is incompatible with so simplistic a specification of the stimulus.

Several perfumers have stated that no two pure compounds have entirely similar and completely indistinguishable odours, and this assertion is based on experience with as many as 15,000 substances, not including mixtures. There must therefore be at least this number of discriminable sensations, and it seems impossible to generate such a number with only seven primary shapes. Subtle variations in the sensation demand equally subtle variations in the stimulus, and this means that olfactory specificity cannot depend on a simple molecular attribute such as the length or cross-section of the molecule.

It is also questionable whether Amoore's odour similarity numbers are as significant a parameter as the verbal descriptions given by expert perfumers⁴. Consider the examples of Table 1.

The details of the molecular parameters underlying this amount of specificity are not known, but a theory of olfaction must develop towards that end. It does not seem possible for the stereochemical theory to achieve this in any of the forms it has taken hitherto.

In his correlation between odour similarity values and the stereochemical similarities, Amoore's estimates of odour similarity are on a scale from 0 for no similarity to 8 for extreme similarity. Examination of his data shows 14 out of 26 similarity values less than 2. It is not clear how far an approximation to "no similarity" is equivalent to an approach to "complete dissimilarity" which would embrace the whole remaining gamut of odours from fried fish to sweet lavender. With more than half his points in this equivocal category, Amoore's correlation loses much of its significance.

Table 1 Comparison of Amoore's Index and Subjective Assessments of Stereochemically Similar Compounds

Compound	Amoore's odour similarity to benzaldehyde	Perfumers' verbal description
Benzaldehyde (standard)	7.14	Bitter almond
m-Ethylbenzaldehyde	1.34	Bitter almond, weak trace of sassafras
m-tert-Butylbenzaldehyde	1.40	Cumin, strong note of carrot
p-Ethylnitrobenzene	2.17	Sassafras, weak note of cumin

It is necessary to remember, too, that a correlation of "A" with "B" (for example, "people who own Rolls Royce automobiles never develop scurvy") does not necessarily signify a cause-and-effect relation. They may be co-causal or associated.

As an illustration of this, it can be shown that Amoore's odour similarity values have a correlation coefficient of 0.85 with the square root of the molecular weight, and of 0.92 with the cube root of the parachor. (The parachor, *P*, is a molecular volume with an allowance for self-compression by intermolecular attraction⁵. As the cube root of volume is length, *P*^{1/3} is an approximation to the molecular diameter.) Indeed, a correlation coefficient of 0.84 can be shown with the lengths of the compounds names.

Contrary to Amoore's claim that the only "realistic" way to compare the vibrational and stereochemical theories is to compute correlation coefficients with his odour similarity numbers, it seems preferable to compare the theories on their ability to predict previously unknown or unsuspected phenomena. The vibrational theory has met this challenge in at least three different ways: the successful prediction of a "green" type of odour on the basis of infrared spectra⁶, the successful prediction of insect (wasp) attractancy in some saturated and aromatic esters⁷ when all previously known wasp attractants were unsaturated aliphatic esters⁸; and the prediction of an "anti-attractant" effect when certain substances, not themselves repellent, were added to known insect lures⁹.

This kind of test is the most stringent and significant way to obtain "a direct measure of which theory fits the olfactory data more precisely".

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A Technique for Studying Sperm Maturation *in vitro*

IN mammals spermatozoa mature while passing through the epididymis. In the rabbit there are virtually no fertile spermatozoa in the caput epididymidis and fertilizing ability is acquired when the spermatozoa pass through the corpus epididymidis^{1,2}. Spermatozoa retained by ligatures, in the proximal corpus develop a normal fertilizing ability in 24 h, but never become fertile when retained for 1 to 12 days in the proximal caput epididymidis^{3,4}. These results strongly suggest that the factors governing the maturation process are not intrinsic to the spermatozoa. To determine whether the development of the

conditions. After 24 h the epididymal tubule placed in organ culture was removed, cut up in 1 ml. Hank's solution and the debris removed. The two sperm suspensions were injected through both uterine walls of one or two does, which were injected with an ovulatory dose of 50 I.U. of human chorionic gonadotrophin (HCG) at the time of insemination. Females were killed 26 h after injection of HCG. The oviducts were flushed and the eggs recovered were examined for the presence of pronuclei or of cleavage, taken as evidence of fertilization. Nuclear details were clarified with acetocarmine staining after fixation in 1:3 acetic alcohol⁵. The male was then killed, the contralateral testis and epididymis removed and the proximal corpus and distal corpus were separated, cut up in 0.5 ml

Table 1 Fertilizing Ability of Spermatozoa from the Corpus Epididymidis Maintained in Organ Culture or in Suspension for 24 h

Male	Control *		Distal corpus Organ culture		Suspension		Proximal corpus Control *		In vitro	
	Motility	Fertility	Motility	Fertility	Motility	Fertility	Motility	Fertility	Motility	Fertility
1	4+§	13/13†	4+	13/13‡	—	—	4+	12/19	4+	7/8
2	5+	10/16	4+	0/7	+	0/5	4+	1/6	4+	7/16
3	3+	10/11	3+	7/7	—	—	2+	0/4	+	0/7
4	5+	5/6	3+	1/1‡	—	—	3+	0/6	3+	0/5
5	4+	8/10	+	7/14	+	0/6	4+	0/7	2+	0/5
6	3+	5/7	2+	4/8	—	—	2+	0/5	2+	0/7
7	—	7/10	—	7/9‡	—	—	—	—	—	—
8	5+	4/16	4+	5/9	—	—	3+	0/10	4+	0/4
9	5+	1/14	5+	0/17	None	0/7	+	0/6	2+	0/5
10	5+	0/18	4+	1/14	None	0/14	4+	0/7	4+	0/5
11	5+	22/24	2+	0/20	+	0/10	—	—	—	—
12	3+	3/3	+	4/6	None	0/10	—	—	—	—
13	+	4/7	2+	8/8	None	0/19	—	—	—	—
Subtotal 1+2								13/25 (52%)		14/24 (58%)
Subtotal 5+12+13				19/28 (68%)		0/25 (0%)				
Subtotal 3 to 13								0/45 (0%)		0/38 (0%)
Total		92/155 (59%)		57/133 (43%)		0/71 (0%)		13/70 (18%)		14/62 (22%)

*"Control" is either the right or left epididymis, the contralateral side is used for *in vitro* culture.

† Number of ova fertilized/number of ova recovered.

‡ Digestion in pronase rather than clostridium peptidase.

§ Motility.

+ Poor general motility.

2+, Circular pattern.

3+, Circular pattern with few forward progression.

4+, Good general motility with many forward progressions.

5+, Excellent forward motility.

fertilizing ability can be achieved similarly when the proximal corpus is maintained 24 h *in vitro* in organ culture, we used the technique described below. Testes were reached aseptically by means of an abdominal incision, and connective tissue and fat were gently peeled from the epididymis of the anaesthetized animal. The tissue was then removed; the proximal corpus and distal corpus were separated and each placed in 1 ml. of a solution of 0.05% pronase or of 0.5% clostridium peptidase for 30 to 60 min at 31° C. The epididymal tubule was gently unconvoluted and placed unbroken on an agar strip. Trowell's⁵ organ culture technique was used with Steinberger's⁶ modification. The medium was Eagle's⁷ minimal medium with 15% foetal calf serum and 100 I.U. penicillin-streptomycin mixture. The gas phase was air containing 5% CO₂, and the cultures were incubated at 31° C, pH 7.0±0.2. A 2 mm segment from the epididymis just distal to the distal corpus was cut up in 0.5 ml. of the same tissue culture medium. The sperm suspension was incubated in a test-tube for 24 h under the same

Hank's solution and the debris removed. Sperm suspensions were inseminated in 1 or 2 does as described above. A total of 13 males and 58 females were used.

Two of 9 males had spermatozoa able to fertilize in the proximal corpus, and the distal corpus; 12 of 13 males had mature spermatozoa in the distal corpus; in the remaining male spermatozoa were still immature in the distal corpus. These results are confirmed by results from a larger group where 13% of 105 males had mature spermatozoa in the proximal corpus and 10% of 135 males had still immature spermatozoa in the distal corpus⁹. Results of inseminations with immature spermatozoa from the proximal corpus, mature spermatozoa from the proximal corpus and mature spermatozoa from the distal corpus are presented in Table 1.

Mature spermatozoa from the distal corpus kept in organ culture for 24 h remained viable in 10 of 13 experiments: When $1.5 \pm 0.4 \times 10^6$ spermatozoa were inseminated, 43% of 133 ova were fertilized. When $1.5 \pm 0.3 \times 10^6$ mature spermatozoa

from the distal corpus of the contralateral epididymis were inseminated, 59% of 155 ova were fertilized. In the 2 males (male 1 and 2 Table 1) where spermatozoa were already mature in the proximal corpus, the same results were obtained: when 1.4×10^6 spermatozoa from the proximal corpus kept in organ culture for 24 h were inseminated 58% of 24 ova were fertilized. When 1.5×10^6 spermatozoa from the proximal corpus of the contralateral epididymis were inseminated, 52% of 25 ova were fertilized. This indicates that mature spermatozoa (from a distal corpus or a proximal corpus where sperm had already become able to fertilize) kept in organ culture for 24 h, maintain their fertilizing ability.

Mature spermatozoa from an epididymal segment immediately adjacent to the distal corpus kept in suspension for 24 h under the same conditions do not remain viable, their motility is very low. When $1.20 \pm 0.07 \times 10^6$ spermatozoa from the lower corpus kept in a test-tube for 24 h were inseminated, none of 71 ova was fertilized (Table 1). If only the males (5–12–13) where sperm survival was very good in organ culture are considered, the failure of the spermatozoa to survive 24 h in suspension in the tissue culture medium is even more striking: 68% of ova fertilized with spermatozoa in organ culture compared to 0% with spermatozoa in suspension. This indicates that the tubules and not merely the spermatozoa survive the culture *in vitro*⁴.

Immature spermatozoa from a proximal corpus kept in organ culture for 24 h remained viable (taking sperm motility as a criterion) but when $1.16 \pm 0.14 \times 10^6$ spermatozoa were inseminated, none of 38 ova was fertilized. When 1.04 ± 0.2 spermatozoa from the proximal corpus of the contralateral side were inseminated, none of 45 ova was fertilized. This indicates that these immature spermatozoa did not gain the ability to fertilize as they do when kept 24 h in the proximal corpus *in vivo*.

These results coupled with the evidence that sperm become fertile in a ligatured proximal corpus of a castrated rabbit only when exogenous testosterone is given⁹ suggest that this phase of sperm maturation is testosterone-dependent. Further work will investigate factors affecting sperm maturation *in vitro*.

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Prehistoric Evidence for *Elephas maximus* L. in Borneo

No undisputed fossil or subfossil remains of *Elephas maximus* L., the Asiatic elephant, have until now been reported from Borneo. The record of *Elephas maximus sumatrensis* from Niah Cave, Sarawak, by Von Koenigswald¹ has proved

erroneous: the phalanx from trench E/B2 (A), dug in 1957, from a depth of 48–60 inches, identified as elephant, belongs instead to *Tapirus indicus* Desmarest^{2,3}. The living *Elephas maximus* from Borneo is generally regarded to be derived from a stock introduced by man around AD 1750 (ref. 4, p. 17).

On a visit to the British Museum (Natural History) in 1967 I examined a portion of an elephant molar, registered as M.10237, from a cavern in Brunei. It looks somewhat fossilized and represents part of a right upper first molar, indistinguishable from its homologue in the recent Asiatic elephant. The entry in the British Museum catalogue reads: "Cavern in Brunei, Belact District, N. Borneo, presented by H. C. Robinson, Esq., May 1910, from the Resident B. O. S. Storey Esq.". Six plates, all worn, are preserved, the cement has gone. The greatest width is 61 mm and the laminar frequency is 8, as in *Elephas maximus* (cf. ref. 5, p. 118). In *Palaeoloxodon namadicus* (Falconer and Cautley), a Mid-Pleistocene species of elephant which is not the ancestor of the extant species and which has been reported from near Samarinda in eastern Borneo⁶, the width of the molar is greater by a lower laminar frequency.

There can be no doubt as to the specific identity of the Brunei fragment, but I thought it expedient to try to determine its geological age. Mrs S. C. Savage has kindly communicated (March 27, 1969) that U₃O₈ determination had given the result 9 ± 1 p.p.m. for the specimen. This is a very high count if it were a recent tooth, or, for that matter, a tooth dating from after AD 1750. Although, as Dr K. P. Oakley has pointed out, this method of relative dating cannot be applied to isolated specimens, it indicates in the present case that the tooth is more likely to be Pleistocene than Holocene. The evidence from the Brunei cavern suggests therefore that *Elephas maximus* was present in Borneo before AD 1750.

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The First Fossil Record of Caecilian Amphibians

THREE groups of amphibians are living today—frogs, salamanders and caecilians. The fossil record of frogs and salamanders is relatively poor^{1,2}, but representatives of most groups have been discovered. For the caecilians, however, no authentic fossils have been recognized, until now. We describe here a single diagnostic vertebra from the Palaeocene of Brazil.

Caecilians are today almost exclusively burrowing animals that are limited to tropical forest regions of South America, Africa and Asia, where few fossil deposits of suitable type are known, so that their absence in the fossil record is partially understandable. Yet the distribution of wet forest conditions was more extensive during the geological past than at present³ and it has been expected that remains of this interesting and little-known group would appear in the fossil records outside their present range. Two supposed fossil caecilians have been described^{4,5} and noted, with reservations, in the most recent revision of the living forms⁶. Several statements as to their validity have been mentioned^{7,8}, but because no documentation of these negative views has yet appeared we provide it here.

A Pleistocene record of a presumed caecilian from Europe was described as ? *Ichthyophis muelleri*, an extinct species of a now Asiatic genus but as has been noted⁶, this specimen cannot be associated with the extant genus *Ichthyophis*. The fossil specimen is a pointed structure with a complex asymmetrical articulation surface at one end (somewhat damaged) and a double row of denticles separated by a groove along one edge, indicating that this fossil is actually the pectoral spine of a silurid catfish. Such spines are usually more slender than this specimen, which appears to be swollen pathologically. The other presumed fossil caecilian was described as *Prohypogeophis tunariensis*, from the Carboniferous of South America, but this specimen is a straight cephalopod (Orthoceratidae) from the Devonian; the serial chambers of the cephalopod were mistaken for the annuli of a caecilian (personal communication to M. H. W. from O. Kuhn in 1968 that the reidentification was made by the late Dr Tilly Edinger, Harvard University, with the agreement of the original describer H. Marcus). Neither of the described records is caecilian, then, and the specimen we describe here is the first authentic record. The unique structure of apodan vertebrae leaves no doubt as to our identification.

The fossil caecilian specimen was discovered in fissure

Etymology: Greek *apodos*, out of tune; *ops*, face: refers to the resemblance to an African genus of this South American fossil. The patronym is for Dr Llewellyn I. Price for his part in collecting and preparing the material for study.

Diagnosis: the specimen most closely resembles vertebrae of the living genera *Geotrypetes* and *Dermophis*, differing from those of the first in the greater extent of the ventral spine, from those of the second in general proportions and greater robustness. It differs from Recent caecilian vertebrae in greater ossification and deepness of blood-vessel grooves. The species diagnosis is the same as for the genus.

Description: the specimen is a single trunk vertebra, complete except for a chip from the posterior edge of the neural arch and breakage anteriorly that has removed most of the structure of the prezygapophyses and the parapophyses. The vertebra demonstrates the former presence of these structures anteriorly and indicates that the parapophyses were relatively very large and directed anteriorly, characteristic of caecilians. The neural arch is low and flattened; broad flanges extend from pre- to postzygapophyses. Two deep grooves extend from the rib-bearing area anteriorly almost to the midpoint of the sides of the neural arch. The neural spine is low and present only on the anterior half of the arch. Postzygapophyses are

Table 1 Vertebral Measurements (in mm) of Fossil and Relevant Recent Caecilians

	<i>Apodops pricei</i> n. gen. n. sp.	<i>Geotrypetes seraphinii</i>	<i>Dermophis mexicanus</i>	<i>Gymnopsis proxima</i>	<i>Typhlonectes compressicauda</i>	<i>Hypogeophis rostratus</i>	<i>Schistometopum thomensis</i>
Centrum length	3.2	3.5	3.8	3.3	3.8	1.8	2.3
Centrum width at constriction	2.0	1.3	1.9	1.1	1.3	1.0	0.9
Parapophysis length	—	1.0	1.7	1.1	1.5	0.8	0.6
Postzygapophysis length	0.9	0.8	0.8	0.8	0.6	0.6	0.6
Total length neural arch including zygapophyses	4.0	4.1	3.9	3.9	5.0	3.1	2.8
Length of neural arch mid-dorsally	3.5	3.3	3.6	3.1	4.0	2.3	2.2
Width at prezygapophyses	3.1	2.7	3.7	2.9	2.5	1.8	1.7
Width at postzygapophyses	3.5	2.5	3.4	2.6	2.3	1.8	1.6
Anterior vertebral height	2.5	2.0	2.9	1.5	1.8	1.3	1.4
Posterior vertebral height	3.2	2.9	3.8	2.3	2.3	1.5	1.6
Centrum height including ventral spine (posterior)	1.8	1.4	2.5	1.3	0.7	0.8	0.8
Centrum height (anterior)	1.7	1.3	1.7	1.0	0.8	0.6	0.7
Centrum width (anterior)	1.1	0.9	1.5	0.8	0.9	0.8	0.7
Centrum width (posterior)	1.5	1.3	1.7	1.0	0.8	0.6	0.7

Apodops pricei, n. gen., n. sp., DGM 551; *Geotrypetes seraphinii*, MVZ 98253; *Dermophis mexicanus*, MVZ 98255; *Gymnopsis proxima*, MVZ 98251; *Typhlonectes compressicauda*, MVZ 98254; *Hypogeophis rostratus*, MVZ 98250; *Schistometopum thomensis*, MVZ 98252. Measurements were made with an ocular micrometer.

fillings in limestone near the town of São José de Itaboraí, Estado Rio de Janeiro, Brazil^{9,10}. Geological factors¹¹ and stage of evolution of the associated mammalian fauna^{12,13} indicate a late Palaeocene age for the fossil. A description of snake, lizard, and frog fossils from Itaboraí is in progress by R. E.

CLASS AMPHIBIA

ORDER GYMNOPIHIONA

Family Caeciliidae

Apodops pricei, n. gen., n. sp.

Holotype: DGM 551, trunk vertebra.

Locality: fissures in freshwater limestone in the quarry of the Companhia Nacional de Cimento Portland (Mauá), São José de Itaboraí, Estado Rio de Janeiro, Brazil. Specimen collected in 1967.

Age: Late Palaeocene.

broad and shallow. The specimen lacks the spinal nerve foramina characteristic of anterior trunk vertebrae of Recent caecilians; this and the general proportions indicate that it came from the more posterior part of the trunk. The centrum is amphicoelous and is markedly constricted at the centre. The cotyles are extensively excavated but the chordal foramina are filled with bone as in Recent caecilians. The centrum bears a pronounced, deep ventral spine throughout its length. The vertebra is robust and heavily ossified.

Measurements: see Table 1.

Discussion: the specimen is unquestionably caecilian, as indicated by shape and proportions of the centrum, neural arch, and ventral spine, and particularly by the large size of the anteriorly-projecting parapophyses. The vertebra is not anuran, because the centrum is long relative to vertebral height and parapophyses are present, and is not urodele, because the transverse processes occur at the anterior end of the vertebra. The vertebra differs from those of Recent caecilians only in the extent of development of the ventral spine, which is longer and

deeper than that of Recent forms examined, and in extent of ossification. The fossil is also more deeply grooved by blood vessels than in most Recent material examined, although this condition is approached by several forms. The specimen has been compared with dried vertebrae taken from the region two-thirds the body length from the head (that is, posterior trunk) of adults of six genera and species (see Table 1), with cleared and stained vertebrae of four additional genera and seven additional species, and with radiographs of another ten genera and twenty-one species. Another fifteen species of five genera examined were either too small for comparison or there were other problems. Thirty-four genera and 158 species of caecilians have been described; we compared material representing twenty genera and thirty-four species from throughout the range of the group.

resemble each other as a result of their similar habitus but we consider this to be less likely.

We believe that the proportions of the fossil caecilian vertebra are of greater significance for assessment of relationships than the robust build and that the fossil caecilian shows actual relationship, as well as similarity, to the African form. Such a relationship is consonant with the hypothesis of continental drift, although it does not confirm it. If this analysis is correct, *Apodops* would be a relict of such a past closer relationship of Africa and South America, because it occurs significantly later than the late Jurassic or early Cretaceous date that has been suggested¹⁴ for separation of the two continents.

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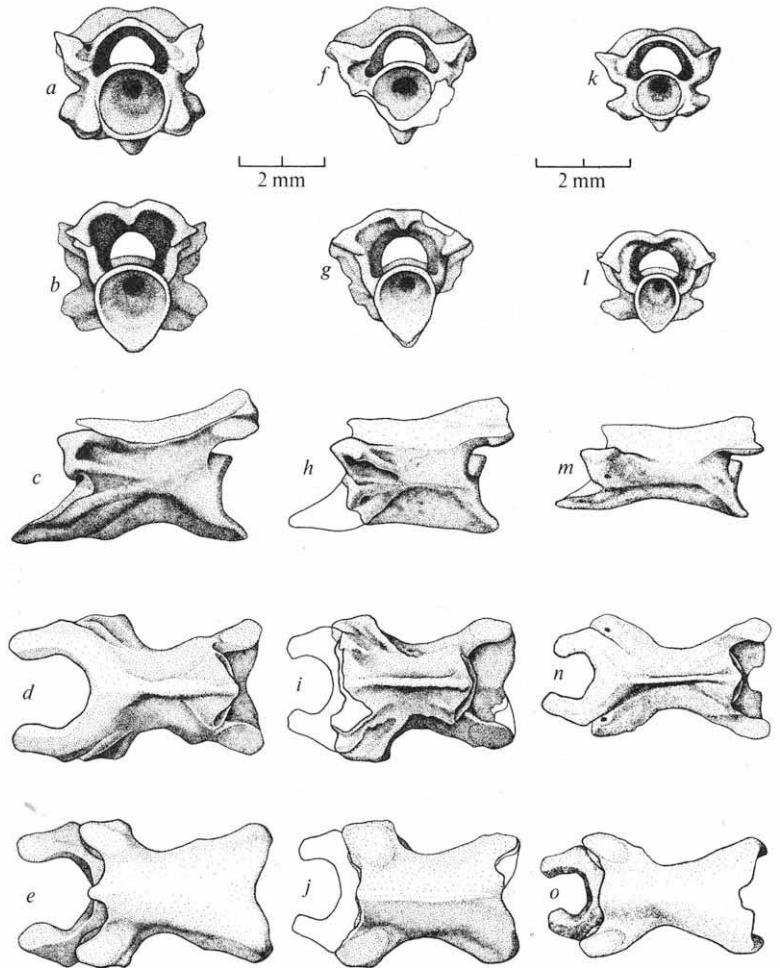


Fig. 1 Vertebrae of fossil and recent caecilians: a-e, *Dermophis mexicanus*, MVZ (University of California Museum of Vertebrate Zoology) 98255, posterior trunk vertebra; f-j, *Apodops pricei*, n. gen., n. sp., DGM 551, the bottom, views are anterior, posterior, left lateral, ventral and dorsal. Anterior is to the left in c-e, h-j, and m-o. Parapophyses and part of posterior border of neural arch are restored in h-j. Magnification line at left refers to a-j; at right to k-o.

Size and proportions of the fossil ally it to the Recent heavy-bodied, terrestrial, viviparous forms. Of the material examined, the fossil vertebra most closely resembles posterior vertebrae of *Geotrypetes*, a west African genus. Size, proportions of the centrum, neural arch, and its processes, and the extent of the ventral spine all indicate similarity. Resemblance to other west African forms, including island species, is less marked. Of Neotropical genera, it more closely resembles *Gymnopsis* and *Dermophis* of Central America than *Siphonops*, now widespread in the region where the fossil was found; resemblance to other Neotropical genera is slight. The robust build of the fossil is very similar to that of posterior vertebrae of *Dermophis*, but the proportional resemblances are with *Geotrypetes*. This does not necessarily indicate alliance with either *Geotrypetes* or with *Dermophis*; the three forms could

Section of the Divisão; and Dr L. I. Price, Curator of Fossil Vertebrates of the Paleontology section, for access to the material in their collections and for help with the preparation of illustrations.

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Culture of Cells from the Urine of Newborn Children

THE increasing importance of amniocentesis for the diagnosis of disease *in utero* has focused attention on the cells obtained by this procedure. Culture of amniotic fluid cells is becoming an established procedure for the identification of foetuses with chromosomal and metabolic abnormalities. Cytogenetic and biochemical studies of these cells in culture and morphological studies of the uncultured cells have shown that they are of

foetal origin¹⁻³. However, the exact origin of the cells which grow remains speculative and several possibilities have been suggested including exfoliated cells from the amnion or from foetal skin^{2,3} and also from the foetal respiratory⁴ and urogenital^{3,4} tracts. Since foetal urine undoubtedly contributes to the amniotic fluid as gestation progresses⁵ it seemed reasonable to assume that some of the cells cultured from amniotic fluid could be derived from the foetal urinary tract.

Samples of urine were collected in sterile bags from four infants less than two days old. For tissue culture, the urine samples were then treated as amniotic fluids; they were centrifuged at 1,000 r.p.m. for 10 min, the supernatant decanted, the cells resuspended in tissue culture medium and then transferred to Petri dishes containing cover slips. Ham's F10 TCM containing streptomycin and penicillin with the addition of 30% foetal calf serum was used. Cultures were incubated at 37° C in an atmosphere of 5% CO₂ in air. Although one culture showed contamination within 24 h, the remaining three were successfully maintained and proliferating cells were first observed at 6, 9 and 10 days respectively. Sufficient cells were present to allow harvesting for chromosome studies at 12 days in the first case and at 17 days for the other two. These culture times are similar to those being obtained at the present time in this laboratory for amniotic fluid cell cultures.

Using light microscopy the cultured urine cells appear morphologically similar to those cultured from amniotic fluid (Fig. 1); but further characterization of these two types of cell strain is required. Cell cultures have now been set up using urines from a total of eight infants aged less than 2 days and of gestational ages ranging from 31 to 40 weeks. Seven of these cultures have produced primary cell strains, one of which has now reached the seventh pass. A small number of cultures from older children have failed to grow. The only previous attempt to culture cells from urine is that of Jacobson and Barter⁴ who set up cultures from sheep urines and bladder aspirates from four human foetuses; however, only one of the former was successful.

The culture of cells from neonatal urine, embodying simplicity in collection and in culture technique, could provide a non-traumatizing procedure for cytogenetic investigations when studies on tissue other than blood are required. Moreover, the most potentially useful application of this technique may be the production of primary cell strains for use in the investigation of inborn errors of metabolism at a biochemical and molecular level.

We thank Dr F. Cockburn for collecting the urine samples.

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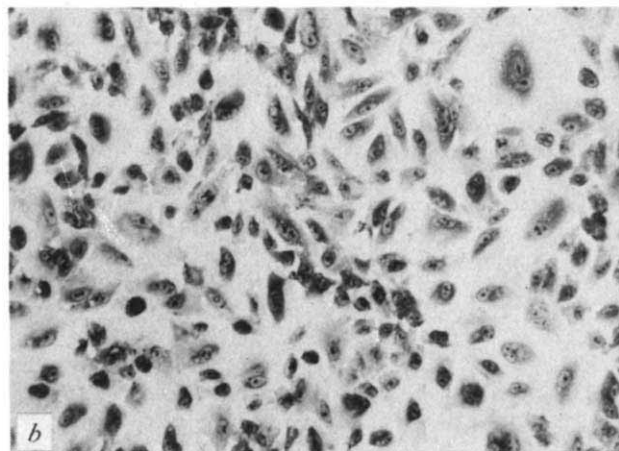
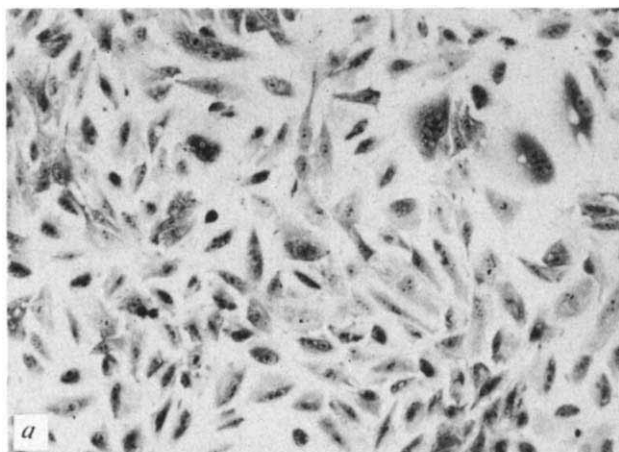


Fig. 1 Cells cultured from (a) urine and (b) amniotic fluid as seen 24 h after the third subculture (stain toluidine blue, $\times 100$).

Effect of Sodium Nitrilotriacetate on Toxicity, Teratogenicity, and Tissue Distribution of Cadmium

MAJOR US detergent manufacturers voluntarily agreed in 1970 to discontinue the use and manufacture of trisodium nitrilotriacetate (NTA), pending further toxicological studies.

This decision was based on the preliminary report that NTA might enhance the matricidal, foeticidal and teratogenic effects of cadmium chloride and methyl mercury chloride in rats¹. NTA itself does not exhibit maternal or foetal toxicity or teratogenicity at levels up to 250 mg/kg/day during organogenesis in rats and rabbits². Several governmental and industrial laboratories have reinvestigated whether NTA enhances the toxicity of heavy metals. We have examined the effect of NTA on maternal and foetal toxicity, teratogenicity, and physiological distribution of orally administered cadmium chloride in rats.

Cadmium is known to interfere with reproduction in rodents. Parizek³ reported that cadmium salts induce a syndrome resembling toxemia of pregnancy in rats at dose levels which were well tolerated by non-pregnant animals. Cadmium salts are teratogenic in the golden hamster⁴ and testicular tissues of rodents are particularly susceptible to the toxic effects of the cadmium⁵. In the mouse, the placenta constitutes a barrier to maternal/foetal transport of cadmium⁶.

In the reproduction study, Charles River COBS female albino rats were mated naturally and mating was confirmed by

was administered with sodium chloride. This trend was not apparent when cadmium chloride was combined with NTA. Foetal body weights were similar among treated and control groups.

The external foetal anomalies observed were oedema and translucent skin. Foetal oedema was observed in eleven pups from dams given 60 mg/kg cadmium chloride plus sodium chloride. The fluid layer surrounding the organ mass was more than 2 mm thick. Three litters from dams given 40 mg/kg cadmium chloride plus sodium chloride and one litter each from dams given 60 or 80 mg/kg cadmium chloride plus sodium chloride exhibited translucent skins. One foetus from dams given 60 mg/kg cadmium chloride plus NTA had translucent skin.

Results of internal teratology examinations are presented in Table 2. Heart and kidney abnormalities were the major internal defects but their incidences were not directly related to the dose of cadmium chloride administered. 20% of all foetuses examined from dams given cadmium chloride plus sodium chloride had atrial defects while the incidence of this defect among pups from dams given cadmium chloride plus NTA was

Table 1 Effect of Oral Cadmium Chloride Plus Sodium Chloride or Trisodium NTA on Reproduction in Rats

Dose levels (mg/kg/day)			Rats (No.)		Autopsy findings mean/female			Foetuses alive on day 19 of gestation				
CdCl ₂	NaCl*	NTA	Pregnant females on gestation † day 6	Suc- cumbed ‡	Corpora lutea	Implan- tation sites	Resorp- tion sites	Total No. of foetuses	Viable foetuses per litter	Viable foetuses/100 implantation sites	Mean weight of young (g)	Externally abnormal (%)
20	40		20	1	12.0	10.3	0.3	191	10.1	97.4	3.8	0
40	80		18	0	12.5	11.3	1.1	184	10.2	90.2	3.7	22.8
60	120		17	2	12.6	10.1	1.5	128	8.5	84.8	3.7	18.0
80	160		18	5	10.7	10.3	3.9	83	6.4	61.9	3.0	15.7
20		62.5	21	0	12.3	10.6	0.8	206	9.8	92.8	3.5	0
40		125.0	20	0	12.4	10.4	1.3	183	9.2	87.6	3.2	1.6
60		187.5	22	0	13.5	12.0	0.8	247	11.2	93.6	3.2	1.6
80		250.0	19	0	13.5	12.6	1.1	217	11.4	90.8	3.7	0.5
Controls (deionized water)			21	0	13.7	10.8	0.5	216	10.3	95.2	3.9	1.4

* Sodium chloride was added at a level to provide a molar sodium ion concentration equivalent to that contributed by the trisodium NTA.

† Charles River COBS rats.

‡ Sodium chloride group is different from NTA group ($P=0.01$). A 2×2 chi-square test was used to compare the proportions of dead mothers at each dose level and summing these components as described by Snedecor and Cochran²⁰.

the presence of spermatozoa in the vagina. Day zero was defined as the day of insemination. Rats were housed in stainless steel cages and had free access to water and a commercial rat food.

Doses were administered orally by gavage to each test animal by means of a hypodermic syringe equipped with a ball-tipped intubating needle. Animals were given 5 ml. test solution per kg body weight per day from the sixth day through the nineteenth day of gestation. Rats were killed by carbon dioxide asphyxiation on the twentieth day of gestation. Incisions were made in the abdominal wall, the uterine horns exposed, and foetal swellings and implantation sites counted. The number of viable foetuses in each uterus was determined using spontaneous movement and ruddy coloration to distinguish live from dead animals. All foetuses obtained were examined for either skeletal or internal development as previously described^{7,8}.

Reproduction data are shown in Table 1. Five deaths occurred among the females given 80 mg/kg cadmium chloride plus 160 mg/kg sodium chloride and three deaths occurred at lower levels of this combination. No deaths were observed among the treated groups given cadmium chloride plus NTA. At autopsy, females in all groups were free of gross uterine abnormalities. The number of viable foetuses per 100 implantation sites tended to be reduced in a dose related manner when cadmium chloride

10%. 15% of all pups from dams given the sodium chloride combination had an ectopic kidney while the occurrence of this defect was 21% among those pups from dams given the NTA combination. 5% of the foetuses examined from dams given 60 mg of cadmium chloride/kg with sodium chloride were hydrocephalic. No hydrocephalic pups were present among those examined from dams given cadmium chloride plus NTA. While there may be differences in foetal anomalies between the treated groups at particular dose levels, there are clearly no statistically significant overall effects of NTA on internal teratology.

Foetal skeletal calcification was delayed in a dose-related manner on exposure to cadmium chloride plus sodium chloride. Sternum sections that were not completely stained with calcium positive Alizarin dye were classified as incompletely ossified or non-ossified section. The combined incidence of foetuses with defective sternum sections was 46% and 30% from dams given cadmium chloride plus sodium chloride and the cadmium/NTA combinations, respectively. There were no other skeletal abnormalities.

In a separate experiment pregnant rats were given single doses of the same cadmium combinations, and cadmium contents and cadmium/zinc ratios determined for several tissues (Table 3). The cadmium contents of livers, kidneys, and

Table 2 Incidences of Congenital Malformations in Rats Receiving Oral Doses of Cadmium Chloride Plus Sodium Chloride or Trisodium NTA

CdCl ₂	Dose levels (mg/kg/day) NaCl	NTA	No. foetuses	Foetuses with internal hydrocephalus (%)	Foetal internal development Incidences of heart* abnormalities (%)	Foetuses with caudal ectopia of kidney (%)	Foetuses with undescended testes (%)	Total abnormal foetuses (%)
20	40		127	0	19.7	15.7	0	30.7
40	80		120	0	11.6	10.8	1.7	21.7
60	120		78	5.1	32.0	21.8	0	46.2
80	160		56	0	28.6	14.3	1.8	44.6
20		62.5	110	0	12.7	24.5	0	31.8
40		125.0	95	0	26.2	15.8	0	42.1
60		187.5	132	0	6.8	16.7	2.3	24.2
80		250.0	112	0	2.7	28.6	0	30.4
Controls (deionized water)			107	0.9	6.6	0	2.8	10.3

* Included small atria, large atria and fibroid heart where: small atria < 3 mm across that transverse section of the heart having the greatest cross-sectional area; large atria < 5 mm across that transverse section of the heart having the greatest cross-sectional area.

Table 3 Concentration of Cadmium and Cadmium/Zinc Ratios in Tissues of Rats 96 h after a Single Oral Dose of Cadmium Chloride Plus Sodium Chloride or Trisodium NTA

Tissue	Cadmium content (% dose/100 g fresh tissue)		Cadmium/zinc ratio ($\mu\text{g Cd} \times 100/\mu\text{g Zn}$ per g fresh tissue)		Control
	CdCl ₂ + NaCl (64 mg/kg + 124 mg/kg)	CdCl ₂ + NTA (64 mg/kg + 200 mg/kg)	CdCl ₂ + NaCl (64 mg/kg + 124 mg/kg)	CdCl ₂ + NTA (64 mg/kg + 200 mg/kg)	
Liver	26.10 $\pm$ 1.67	7.62 $\pm$ 1.29 *	73.4 $\pm$ 6.5	28.8 $\pm$ 4.8 *	0.25 $\pm$ 0.02
Kidney	5.06 $\pm$ 0.37	1.98 $\pm$ 0.28 *	26.2 $\pm$ 2.1	10.0 $\pm$ 1.1 *	0.45 $\pm$ 0.03
Muscle	0.106 $\pm$ 0.006	0.052 $\pm$ 0.004 *	0.91 $\pm$ 0.04	0.54 $\pm$ 0.03 *	0.25 $\pm$ 0.03
Foetus	0.050 $\pm$ 0.008	0.038 $\pm$ 0.008	0.48 $\pm$ 0.06	0.28 $\pm$ 0.06 †	0.32 $\pm$ 0.04

Values are means of duplicate analyses on tissues from ten dams per treatment and three dams in controls. Foetal values are means of six foetuses per dam $\pm$ s.e. of the mean†.

* Significantly different from CdCl₂ + NaCl value, $P < 0.01$ by analysis of variance using one-way layout design.

† Significantly different from CdCl₂ + NaCl value, $P = 0.05$ by analysis of variance using one-way layout design.

‡ Pregnant Wistar strain rats varying from 1–3 days' gestation period were used and dosing was carried out exactly as in the reproduction study at a time corresponding to the fourteenth–sixteenth day gestation. Sample collection, preparation and atomic absorption spectrophotometric analyses for cadmium and zinc were carried out exactly as reported previously¹⁰.

muscles of rats given cadmium chloride plus sodium chloride were higher than those from rats dosed with cadmium chloride plus NTA. These results are consistent with data showing the inhibition of cadmium deposition in target organs by ethylenediaminetetraacetic acid (EDTA)⁹ and NTA¹⁰ in rabbits and non-pregnant rats, respectively. The cadmium content of foetuses from dams dosed with cadmium chloride plus NTA, however, did not differ significantly ($P = 0.10$) from the cadmium content of foetuses from dams dosed with cadmium chloride plus sodium chloride.

Cadmium is a known zinc antagonist^{11–14} and may result in high cadmium/zinc ratios which have been associated with a wide variety of chronic diseases^{15–18}. High cadmium/zinc ratios were found in tissues of animals exhibiting shortened life spans, arterial hypertension, heart disorders, and toxemia of pregnancy¹⁹. Cadmium/zinc ratios in liver, kidney and muscle of animals dosed with either cadmium combination were substantially higher than the cadmium to zinc ratio of organs from control animals. The ratios in these tissues, however, were lower in animals dosed with cadmium plus NTA than in animals dosed with cadmium plus sodium chloride. The cadmium/zinc ratio of foetuses from dams dosed with cadmium and sodium chloride tended to be higher than the cadmium/zinc ratio in foetuses from dams dosed with cadmium plus NTA or control animals.

Our findings show that orally administered cadmium chloride during pregnancy was toxic to the mother and was teratogenic in rats. Consistent with these results was the observation that single doses of cadmium accumulated in the maternal tissues which increased the cadmium/zinc ratio of the maternal tissues and foetus. Oral administration of NTA with cadmium chloride provided protection against the matricidal effect of cadmium ($P = 0.01$) and had no effect on the teratogenicity and foetal accumulation of cadmium. Further, NTA inhibited the deposition of cadmium into maternal tissues ($P = 0.01$) and the associated increases in the cadmium/zinc ratios of liver, kidney, muscle and foetuses.

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GENERAL

Reply to H. V. Wyatt

WYATT's inference¹ that Avery's work on pneumococcal transformation was not well recognized by geneticists in the decade following his 1944 report² is somewhat at odds with my own recollection and experience. If we sometimes omitted a specific citation to the original work, this is testimony to his name (like Mendel's) having already become a household word, too familiar to require routine attribution. A more useful reference might be a later review.

In 1946, at the Cold Spring Harbor Symposium, where Tatum and I first reported³ on recombination in *Escherichia coli*, we were incessantly challenged with the possibility that this was another example of transformation, à la Griffith⁴ and Avery². In October 1946, we simply referred⁴ to negative experiments on transformation with filtrates. These trials were not, in our judgment, detailed enough to warrant comparison with Avery's formidable precedent.

In 1947, we reported⁵ on these experiments more fully, including the lack of effect of deoxyribonuclease, and cited Avery². We at no time doubted that geneticists were aware of the pneumococcus studies. In 1951, I included ref. 2 in a collection of reprints intended for graduate students in microbial genetics⁶.

One vignette⁷ that has not appeared in the scientific literature is that my first laboratory work with F. J. Ryan was an attempt to emulate Avery by transforming *Neurospora* mutants with DNA extract. This was unsuccessful, and was therefore regarded as unworthy of report. These experiments, however, did lead to the finding⁸ of reverse-mutations of auxotrophs in *Neurospora*, and the same selective methodology led subsequently to the discovery of recombination in *E. coli*.

Until Hotchkiss⁹ had reported the independent transfer of diverse markers by pneumococcal DNA, and comparable phenomena had been elaborated with virus-mediated transduction, the biological interpretation of the underlying phenomena lay in doubt. This was prolonged by the optimism (or obscurantism) of some of my biochemical colleagues who

refused to correlate these findings with the tradition of Mendelian genetics. Avery's own a-theoreticism¹⁰, while admirable for its modesty, nevertheless contributed to the postponement of the conceptual synthesis that now identifies "gene" with DNA fragment. This implication was, however, clearly enunciated by some of our most influential geneticists, such as Muller¹¹ and Wright¹². (Wyatt quotes an ambiguous comment from Wright's paper, but omits the crisp assertion: "The results suggest chemical isolation and transfer of a gene . . .".) A history of these interpretations has been embodied in several of my own reviews written during the period¹³⁻¹⁵. Unfortunately, we do not have a comprehensive Citation Index for the period before 1961, which would facilitate the accurate documentation of the influences of the pneumococcus work.

More remarkable than the neglect which is imputed (in my view incorrectly) to Avery's work since 1944, is the failure of other microbiologists and geneticists to explore the Griffith phenomenon¹⁶ between 1928 and World War II. More undisciplined or better informed speculation might have encouraged experiments with a wider variety of genetic markers; these studies were technically possible at least 20 yr before they were attempted. It would also be of interest to know more than Griffith told us by his own bibliography¹⁶ of the conceptual antecedents that may have inspired his experiments. An ancient literature readily available to Griffith, but whose exhumations^{17,18} are now themselves rather mouldy, records a number of observations that may deserve further attention, even today. An example is the serological cross-reactions of rickettsia with the bacterial strain, *Proteus* OX-19. These were naively attributed to a biological relationship, the *Proteus* strains having been isolated from typhus patients. The relationship may indeed be fortuitous¹⁹, but it has not been studied with modern techniques. For another example, see ref. 20.

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BOOK REVIEWS

Mendelism v Darwinism

The Origins of Theoretical Population Genetics. By William B. Provine. Pp. xi+201. (University of Chicago: Chicago and London, December 1971.) £2.50.

DARWIN believed that evolutionary change occurs by natural selection of small individual differences appearing every generation within any species. Singly the changes effected by selection are small, but given enough time great changes can take place. Two of Darwin's most dedicated supporters, Thomas Huxley and Francis Galton, argued instead that evolution occurs by selection of discontinuous variations, or sports; evolution proceeds rapidly by discrete leaps. According to Huxley if natural selection operates only upon gradual differences among individuals, the gaps between existing species and in the palaeontological record could not be explained. For Galton, "The process of evolution is not a smooth and uniform progression, but one that proceeds by jerks . . . some of them implying considerable organic changes."

This controversy was continued in the latter part of the nineteenth century by the biometricians Karl Pearson and W. F. R. Weldon, who believed like Darwin in the primary importance of common individual differences, and by William Bateson who maintained the primary importance of discontinuous variations. The dispute generated intense personal animosity between Bateson on one side, and Pearson and Weldon on the other, and that made it impossible for each side to see the part of truth in the antagonist's position. This was particularly unfortunate because the rediscovery of Mendelian inheritance in 1900 provided what might have been common grounds to resolve the conflict. Instead, the dispute extended to continental Europe and to the United States. Bateson was the champion of the Mendelians, many of whom accepted the mutation theory proposed

by De Vries, and denied that natural selection played a major role in evolution. The biometricians for their part argued that Mendelian characters were sports of little importance to the evolutionary process.

The conflict between Mendelians and biometricians was resolved between 1918 and 1931 by the work of R. A. Fisher and J. B. S. Haldane in England, Sewall Wright in the United States, and S. S. Chetverikov in Russia. Independently of each other, these authors proposed theoretical models of evolutionary processes which integrate Mendelian inheritance, natural selection, and biometrical knowledge. Modern evolutionary genetics is based on their work.

Provine's book is an excellent account of the long and tortuous gestation period of population genetics, which started with the publication of *The Origin of the Species* and ended seven decades later. The book is informative and readable. Provine points out that his story illustrates some important patterns in the history of science. One pattern is that the acceptance by scientists of new ideas sometimes depends more on *a priori* preconceptions than on their scientific proof. One example is the pure line theory which played such an important role in the controversy. "It was accepted, as well as the selection theory associated with it, by almost all geneticists even though conclusive experimental proof was totally absent." Perhaps the most important lesson to obtain from this story is that personality conflicts are sometimes decisive in the development of scientific ideas. One can only agree with Provine's conviction that "The intense antagonisms generated by Bateson's dislike of Pearson and Weldon and *vice versa* contributed to a delay of more than a decade in the understanding that Mendelism and Darwinism were complementary."

G. B. Shaw wrote that "we learn from history that men never learn anything from history." Population genetics has continued to be plagued

with acrimonious controversies fueled by strong personal animosities. Some controversies are still with us, like that concerning the adaptive significance of genetic variation observed at the molecular level. Population genetics may progress faster if those involved in this or other controversies make every effort to see what part of truth may exist in the antagonists' position. It may be worthwhile to learn from history and prove Shaw wrong.

FRANCISCO J. AYALA

Physical Fairyland

Modern Aether Science. By Harold Aspden. Pp. 165. (Sabberton: Southampton. 1972.) £2.50 hard cover: £1.25 paperback.

WITH the word "aether" in the title, one would expect this book to conflict with much of conventional modern physics. In fact, it conflicts with even the fundamentals of accepted scientific practice. For Dr Aspden is one of a group of unorthodox writers who, bewildered by the abstract but precise world of mathematical physics, escapes into a fairyland of outmoded physical description as he appeals to concepts sufficiently unfamiliar and vague to enable him to concoct an "explanation" for almost any physical phenomenon.

The author openly admits that he does not understand most of what is, for the professional scientist, standard undergraduate physics. The total lack of mathematics in this book is deliberate. Nature's simplicity, writes Dr Aspden, must preclude such "occult magic". Consequently the ambitious programme of constructing a completely revolutionary form of physics conveniently provides no hard numbers to check against experiment. What the author appears to have overlooked is that the first task of a new theory is to explain adequately the correct features of the old. Instead of this, all of con-

ventional relativity, electrodynamics, gravitation, atomic and nuclear physics are swept away for the apparent reason that the author does not understand them. They are replaced by a hotch-potch of pseudo-scientific jargon that will mean very little to the orthodox scientist. Apart from UFOs and ball lightning (always good to throw in the face of orthodoxy) nearly all of the phenomena discussed in the book already have perfectly acceptable explanations, so it is hard to understand the motivation of the work.

No doubt many laymen will enjoy this polemical assault on the humble scientist, who is portrayed here as a sort of space age wizard juggling meaningless symbols to conjure up incomprehensible results. This book will be of no use, though, to anyone seriously interested in either the aether or good science. PAUL DAVIES

Harnessing the Tides

Tidal Power. Edited by T. J. Gray and O. K. Gashus. (Proceedings of Tidal Power, held May 24–29, 1970, at the Atlantic Industrial Research Institute, Nova Scotia Technical College, Halifax, Nova Scotia.) Pp. 630. (Plenum Press: New York and London, 1972.) \$32.20.

THE ever increasing demand for electrical power on the one hand and concern for the quality of the environment on the other has led to a reappraisal of the world's tidal power potential. This book is the proceedings of an international conference on the subject, held in Halifax, Nova Scotia, in 1970. Because of this venue, it perhaps is not surprising that the first four papers explore many aspects of tidal power in the context of the Bay of Fundy proposals. A less specific introduction might have been preferable, but it can be argued that discussion of tidal power can rarely be divorced from particular topography. The complexities and benefits of this power source are further brought out in descriptions of existing or projected plants in France (La Rance), Russia (Kislaysa Guba), the Argentine (San José) and Alaska (Cook Inlet). Problems associated with the integration of tidal power into a general supply network and the interesting possibilities of linking tidal power closely with pumped storage are the subjects of the next five papers. Methods of barrage construction, notably those in vogue in the Netherlands, design of sluice gates and the evolution of the straight flow turbine (a critical factor in the economic viability of tidal power) are then dealt

with in four contributions. Three chapters are devoted to the important topic of the behaviour of concrete, ferrous and non-ferrous metals in a marine environment. An oddly placed but useful chapter poses a number of questions, mainly of constructional and operational nature, which require further research and evaluation. Environmental effects receive attention both in broad terms and in relation to specific locations. In particular, siltation is a recurring theme, one paper dealing with a mathematical study of siltation in the Thames estuary (not, however, linked with power generation). Discussion sessions of the conference are not reported and some valuable comment and observation may have been lost. Inevitably, because of the number of contributors, the book suffers from restatement of basic principles, and requirements, but, on the credit side, each contribution has something refreshing to add. Little attention is paid to model studies and there are one or two significant omissions in the historical references; for example, no mention is made of Gibson's investigation of the Severn Barrage scheme. The volume, pleasingly printed and well illustrated by line diagrams, photographs and graphs, forms a valuable, if expensive, record of current thinking on tidal power.

GEORGE D. MATTHEW

Aspects of Atmosphere

Thermospheric Circulation. Edited by Willis L. Webb. Pp. xix+372. (MIT: Cambridge, Massachusetts, and London, March 1972.) \$14.95.

Physics of the Upper Atmosphere. Edited by Franco Verniani. (International School of Atmospheric Physics, Proceedings of the 1st Course, Erice, June 15–29, 1970.) Pp. xxiv+461. (Editrice Compositori: Bologna, 1971.)

THE Earth's upper atmosphere continues to be a topic of lively research interest and the above proceedings of two 1970 summer schools on the subject have recently been published. The first was held at the University of Texas at El Paso in cooperation with the Atmospheric Sciences Laboratory, US Army Electronics Command, White Sands Missile Range, and the second at the "Ettore Majorana" Centre for Scientific Culture sponsored by CNR (the Italian National Research Council), the Italian Ministry for Public Education and the Regional Sicilian Government.

The interdisciplinary character of many rewarding areas of research is well exemplified by the atmospheric sciences, which involve physics,

meteorology, aeronomy, chemistry, radio engineering and space science. In the foreword to the first of these books, Fred L. Whipple refers to "... interface phenomena, partly or wholly arising from external radiation or particles from space impinging on our own private space ship, the Earth". The book, however, is entitled *Thermospheric Circulation*, which is defined in the opening chapter as "the geocirculation system which occupies the atmospheric region above 80 km altitude". Not surprisingly, six of the fifteen chapters are devoted to the radio-meteor trail method of wind measurement. This is the only continuous means of wind measurement that is available above 80 km and offers the possibility of synoptic study of the atmosphere to 110 km. The remaining chapters contain condensed reviews on the airglow, noctilucent clouds, the lower ionosphere and its interaction with the neutral atmosphere, and the topside ionosphere. The content of the book, however, falls far short of what one might expect from the title. On the observational side, circulation in the upper thermosphere has been revealed by rocket trail releases and the analysis of satellite orbital inclinations; while on the theoretical side, computations of thermospheric winds have been carried out with various assumptions regarding the effects of ion drag and viscosity. These topics are not included. *Thermospheric Circulation* is a pot-pourri of basic lower thermosphere physics and status reporting on radio-meteor wind measuring techniques and results. The book is printed offset and has no index.

Physics of the Upper Atmosphere also emphasizes the interdisciplinary character of the Earth's upper atmosphere. Composition studies of the lower ionosphere are well covered by R. S. Narcisi. M. Petit deals with basic physical processes of ions and electrons in one chapter, which serves as a basis for a chapter on Thomson scatter—the incoherent scattering of electromagnetic waves from free electrons. This technique is now providing valuable data for studying many properties of the ionosphere. A chapter by F. Mariani treats the theory, observation and measurement of the geomagnetic field with notable conciseness and clarity. Chapters by P. W. Blum and M. Roemer deal with the density and temperature structure of the thermosphere as understood from satellite drag effects and time-dependent models. Theory on the dynamics of the upper ionosphere is found in a chapter by M. Sylvain. The book deals with basic physical principles and their applications to current research, and could usefully be read as an introduction to current research papers. Not included are topics such

as high-latitude phenomena, ionospheric irregularities and processes of a morphological nature. The reader may therefore gain the impression that the upper atmosphere is better "ordered" and complies more closely with theory than is actually the case. The book is printed offset and contains author and subject indices. G. V. GROVES

Rethinking Logic

Mathematical Introduction to Logic. By Herbert B. Enderton. Pp. xiii+295. (Academic: New York and London, April 1972.) \$12.50.

ALTHOUGH mathematical logic has been established for many years as a fundamental mathematical discipline, access to it through textbooks is still difficult. *Principia Mathematica* and the other great classics of the early days are now historical monuments; and the more severely mathematical treatments of logic and metalogic that were inspired by Hilbert have also an old-fashioned air. This is true even of Hilbert and Bernays's definitive *Grundlagen der Mathematik*, a work which, by virtue of its profundity and its comprehensiveness, has been the bible of generations of mathematical logicians. Since the 1930s many fundamental advances have been made by logicians, and a new spirit of formal thought has permeated logic as well as mathematics. Unfortunately, the demand for formal rigour has made the more recent books decidedly formidable and often of use only to experts; and some of the best of them have in fact been the most unapproachable. What is urgently needed is a Hilbert-Bernays for today, in which all the central ideas and results of logic are presented intelligibly and yet authoritatively in current language, and their relevance to the mathematics of the modern working mathematician is clearly brought out. It is just such a book that Professor Enderton has written; and the sureness with which he has grasped the need, and himself met it, is remarkable. He has not just refurbished once again an outworn tradition, but has rethought everything from the beginning and then presented his account with lucidity and elegance. The old question of consistency, so important for Hilbert, is now dead, and Enderton allows decidability to inherit its role; but the substance of Hilbert and Bernays's metamathematics still lives on, as conservative readers will be encouraged to find, though in a changed context. Among the post-Hilbert sections of the book is a particularly welcome one on nonstandard analysis.

G. T. KNEEBONE

Rare Earth Solids

Physics of Rare Earth Solids. By K. N. R. Taylor and M. I. Darby. Pp. xi+308. (Chapman and Hall: London, April 1972.) £7.

IN this book the authors have taken upon themselves the unenviable task of attempting to give an up to date review of the physics of rare earth solids. They have placed particular emphasis on the physical properties of rare earth metals and alloys as well as their metallic and non-metallic compounds. The presence of a bibliography involving 826 references testifies to the enormous amount of material the authors have had to sift through in preparing their review.

The success, or otherwise, of such a review must surely depend on the degree to which the authors have made a critical appraisal of the material reviewed, indicating both the strengths and weaknesses of current models together with some assessment of present trends and directions future researchers are likely to pursue.

The opening chapter on ionic properties, as a review, is disappointing and gives the impression that the authors are perhaps not as familiar with the material referenced as they might be. The bottleneck effect for the Orbach process, observed in 1969, is reported as unobserved while calculations for Sm^{3+} and Er^{3+} in LaCl_3 are claimed to be made without overlap when indeed they were presented with overlap. Their discussion of the spin-orbit interaction and its effects is particularly confused. A spot check of the references revealed a number of inconsistencies, as for example in the citing of reference 3 as a source of information on fractional parentage while at the same time ignoring the important tabulation of Nielson and Koster.

The authors are clearly more at home in the succeeding chapters but at times have an uncritical approach to some of their material. That the use of a free electron model in the RKKY interaction has, as the authors state, led to an understanding of many of the properties of the rare earth metals seems somewhat fortuitous in the light of relativistic APW calculations of band structure. A similar situation arises in the discussion of the Hartree and Hartree-Fock methods. Unfortunately wrong models can all too often give "correct" results for the wrong reasons, and seem to have led the authors into the trap of J. L. Synge's appropriately named Pygmalion syndrome.

The authors handle much of their material competently and have certainly collected together many widely dis-

persed data and given them a compact presentation. As such their book is likely to constitute a valuable source book to rare earth researchers and be warmly recommended for most physics and chemistry libraries, though many readers will need to refer to the original literature for adequate details.

B. G. WYBOURNE

Biology as Chemistry

Introduction to Molecular Biology. By S. E. Bresler. Translated by Robert A. Zimmerman. Pp. xv+556. (Academic: New York and London, 1971.) £8.50; \$17.50.

MOLECULAR biology is an area of science in which a plethora of techniques from physics, chemistry and biology is used to probe the chemical nature of biological phenomena. Because of this vast diversity most authors of recent textbooks in molecular biology have confined themselves to a relatively small area of the subject. Not so Professor Bresler, who has taken on the immense task of writing a comprehensive text of molecular biology.

The book is divided into five chapters, each of approximately one hundred pages, dealing with protein structure, protein function, nucleic acid structure, DNA function and RNA function. There is a strong emphasis throughout on the application of mathematical and physical techniques, every opportunity being taken to introduce the chemical and thermodynamic background to biological phenomena. Thus, for example, the account of the classical Meselson-Stahl experiment is accompanied by a lengthy discussion of the theory of density gradient centrifugation, and the description of DNA replication includes a calculation of the free energy barrier against mistakes in that process.

A single volume of five hundred pages obviously cannot deal with the whole of molecular biology in any great depth. Professor Bresler's treatment is intended more as an introduction to the subject for students with a strong background in physical sciences and mathematics; students without this training would probably find the approach unsympathetic. The balance of the book naturally reflects the author's specialist interests. The chapters on proteins are very well presented, structure and function being most convincingly inter-related. The chapters on nucleic acid function seem less detailed and less authoritative. It is this section which also suffers most from being out of date; the literature survey ends early in 1969.

Errors are rare and usually trivial,

though the section on temperate phages manages to preserve several old misconceptions and to propagate some new ones. The presentation does tend to create the unfortunate impression that most of the important questions in molecular biology have already been answered, and it seems a great pity that no attempt was made to stimulate the reader to think about some of the exciting problems ahead.

In spite of its faults, many of which seem inevitable in a text of this scope, Professor Bresler's book should serve as a sound introduction to the subject for anyone with the appropriate background.

W. J. BRAMMAR

Chemical Engineering

Physical Principles of Chemical Engineering. By Peter Grassman. Edited by Dr H. Sawistowski. Translated by R. Hardbottle. Pp. xxx+896. (Pergamon: Oxford and New York, December 1971.) £16.

It has never been easy to define the boundaries of chemical engineering and the great attraction in the practice of the profession is that it demands the gathering together and assessment of a project by using data from a wide range of considerations, including technical and economic. In the United Kingdom the strong growth of the subject as an educational discipline took place from the mid 1940s and the courses then developed were strongly influenced by American texts. There were two main pillars to these courses, the strong influence of physical chemistry and the strong wish to get to the teaching of technology in a form directly helpful for training in the design of equipment. The problem of providing a widely based scientific training coupled with a forward looking technological content could not really be resolved and is still elusive to the three-year degree courses so common in this country.

It was not till Bosworth wrote his *Physics in the Chemical Industry* that the very significant part played by physics was sharply brought out but it has not been found easy to include a course of basic physics in our chemical engineering courses. This text by Professor Grassman is welcome not only because of its actual content but because it emphasizes the vital importance of physics and in so doing brings a very different approach to much of the subject compared with that offered by the majority of existing texts.

On the European continent the belief in giving a long course in science to engineers has enabled their centres to provide for a course with a basic physics flavour fitting into the fourth or fifth year of the course. It is difficult to

see how this kind of study can be fitted into any undivided form of three-year course, but it is well to remember that this is lacking from these shortened British courses.

In this treatment based on physical principles, all operations governed by the same aspects of physics are considered together, giving a more generalized analysis than that provided by the concept of "unit operations", but such an approach is in no way engineering in outlook. This form of thinking is implied by the titles to such chapters as (10) "Multiphase Flow Processes", or (7) the "Applications of Fluid Dynamics". The former covers filtration, fluidized beds, gas bubbles in liquids, atomization, foams, emulsions as well as two phase flow in pipes.

An indication of the contents is given by considering some of the chapters. Thus the first three chapters "Mass and Energy Balances", "Concept and Use of Energy", and "Probability Theory and the Kinetic Theory of Gases" indicate well the basic physics and the section on Maxwell's velocity distribution and that on diffusion provide a particularly stimulating discussion. Chapter 5 on "Bodies with Large Surface Areas" covers porosity, size, shape of particles, drop size distribution of liquids, packings, and a refreshingly interesting discussion on the efficiency of size reduction. Chapter 7 on "Applications of Fluid Dynamics" covers flow in pipes, eddies, mixing, residence time distribution, turbomachinery, design principles of pumps and compressors.

Whilst there is no special chapter on either heat or mass transfer chapter 9 covers heat, mass, and momentum transfer, taking every possible opportunity to indicate the similarities and differences. Thus the section on boiling liquids contains a discussion on the really basic problem of nucleation, in many ways a mass transfer problem. Again the dimensionless groups in heat and mass transfer are considered together and used to discuss turbulent transfer.

Chapter 11 on rheology shows the extending nature of the subject and chapter 4 on the physics of solids although too concentrated does raise a number of problems not commonly discussed.

This text although in the *Chemical Engineering* series will prove of considerable value in some of the modern courses on engineering and science and it will also prove helpful to those mechanical engineers who wish to have a much better understanding of their own processes. It is not an easy text to read but the reader who wishes to dig into the real problems that are so often glossed over will benefit and find it stimulating and thought promoting.

This form of presentation will also

prove useful to advanced students and to those teachers who are seeking inspiration and a new approach to their subject. We must therefore thank Pergamon Press for bringing to our notice another European text.

Dr R. Hardbottle, the translator, and Dr H. Sawistowski should both be congratulated on their valuable contribution to this study.

J. M. COULSON

Phonons in Crystals

Thermodynamics of Crystals. By Duane C. Wallace. Pp. xviii+484. (Wiley: London and New York, April 1972.) £8.85.

THE scope of this book is narrower but deeper than its title may suggest. It concentrates on the theory of those thermodynamic properties of perfect crystals which are vibrational or electronic in origin, excluding such topics as phase transitions and interactions with electromagnetic fields. In compensation, it expounds the theory of vibrational and electronic effects starting from ion cores and outer electrons. The result is a successful vertical integration of the thermodynamics of solids and its fundamental theory, in a manner not previously attempted.

The author is an expert on the topics he discusses, so that this book is self-contained and authoritative. The theory is comprehensive: for example, it treats both renormalized and self-consistent phonons, as well as electron-phonon interactions. At the same time, there is an emphasis on results suitable for numerical work, with a chapter on model calculations and an appendix on computational techniques. Unfortunately, the book is self-contained to a degree which entails loss of perspective, particularly in the paucity of references to alternative nomenclature and methods. The reader finds thermal expansion coefficients called thermal strain coefficients after one explanation, and what he may know as thermodynamic tensions and effective harmonic frequency spectra never referred to as such. Ideas are elusive entities, not easily indexed and abstracted, and hence especially dependent on full documentation in books, yet here references occur on average only every twelfth page (ignoring the author's self-citations). Experimental data, on the other hand, though more accessible in the literature, are here both documented and tabulated after use in one chapter.

Notwithstanding the idiosyncrasies, *Thermodynamics of Crystals* fills a gap in the literature, and makes profitable reading for anyone concerned with thermal and elastic properties of solids.

R. W. MUNN

CORRESPONDENCE

British Optical Astronomy

SIR,—Dr Burbidge's highly personal account of his likes and dislikes in British astronomy provides the occasion for comment that may prove more constructive.

I have myself sometimes been critical of British astronomy, and can agree with some of Dr Burbidge's historical comments, although in my view the chief fault has been undue deference to the supposition (probably mistaken anyway) that a large "prestige" telescope was politically more acceptable than the diversity of an observing system optimized for cost-effectiveness. Although having reservations about site testing¹, where Dr Burbidge criticizes the sites of British telescopes I would tend rather to question the design of the telescope itself. The Anglo-Australian Schmidt for example appears to be designed for survey work and to lack the accuracy needed in a production instrument, so far as can be surmised from the information publicly available.

Times have changed, however, and the new generation of British astronomers that has become influential in recent years is unlikely to repeat the old mistakes, which are now accordingly largely irrelevant. In common with all who try to do something creative, these astronomers will make new mistakes of their own which it will be the task of the next generation to correct. The conditions that led to the long delays in the Isaac Newton Telescope no longer prevail, and indeed some of the questionable decisions were more the responsibility of Government and Treasury policy at the time than the free choice of the astronomical establishment, however complacent or misguided it may have been.

Of course much in British optical astronomy is third rate, as is much in American astronomy or for that matter much of anything in any country. The normal criterion is to look at what stands out, and here British astronomy need have no fear of international comparisons. GALAXY² was developed for less than one-tenth of the probable cost of the 90-inch telescope alone in Dr Burbidge's proposals, and in a couple of years has about doubled the number of accurate positions and magnitudes ever measured in the history of astronomy. These data are giving new insight into the structure of our Galaxy; if it were not so, would not the failure be in the theoreticians? No basis is given for the assertion that

GALAXY has attracted no overseas interest, but I happen to know personally of firm enquiries from both Europe and the Americas. The Radial Velocity Photometer³ has in a similar period enabled one man, working by himself from latitude 52° N and reducing his own data, nearly to double the number of first quality radial velocities known, including a programme of Southern stars. Multiplex Spectrometry⁴ developed internationally from British origins, has provided spectra of Venus and Mars of higher quality than standard solar atlases. The Spectracon⁵ has enhanced by several times the potential of every telescope in the world for some kinds of observation. Further examples will occur to others familiar with other aspects of British optical astronomy; but indeed apologists are not needed for what already speaks for itself.

Experience teaches that complex problems are seldom solved by pursuing a narrow "single goal", and Dr Burbidge's proposals would be suspect for this reason alone. It is moreover ironic that he proposes to copy the American large-reflector tradition, since the West Coast reflectors were developed from the "3-foot" Common reflector presented by Mr Crossley of Halifax to the University of California at the turn of the century. It is at least possible that British astronomers have by now seen beyond this "British, and hence unproven, astronomical innovation" and may wish to do something else.

It is odd also that Dr Burbidge questions qualifications in observational astronomy, while as a theoretician telling British observers and instrument scientists what they ought to do. Astronomical knowledge does not progress in this way, but by a two-way exchange in which observation and theory work together in posing and solving astronomical problems. The synthesis of more effective methods of observation requires mutual interaction in which instrument scientists, observers and theoreticians each contribute from their own knowledge and professional specialization. These developments flourish best when there is free, wide and open discussion, no pre-emption by decisions made behind closed doors, and when the scale of each project is not so large that it must try to please everyone and perhaps ends by pleasing no one.

For these reasons, Dr Burbidge's letter has encouraged me to believe that British optical astronomy is basically

healthy just because it is not committed to the particular approach which he favours.

Yours faithfully,

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⁴ Fellgett, P. B., Thesis, Univ. Cambridge (1951); *J. Phys. Radium*, 19, 187 (1958); Connes, P., *Optica Acta*, 4, 136 (1957); Connes, J., Connes, P., and Maillard, J. P., *Atlas des spectres dans le proche infrarouge de Venus, Mars, Jupiter and Saturne* (Editions de CNRS, Paris, 1969).

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Refereeing and Editing

SIR,—Here is a suggestion for doing away with the refereeing and editing of papers in scientific journals, for reducing the time and cost of publication and for improving the general standard of presentation.

In principle, the idea would be to put at the disposal of an author in any one year a stated number of pages to publish anything he chooses with no refereeing and no editing. More accurately, the idea would be to credit an author with a number of pages and constrain him (or his institution) to do the refereeing and editing. The scheme could therefore be called ACRE (Author Credit, Refereeing and Editing).

In practice, ACRE could be initiated by the publishers (societies and firms) of several leading journals; afterwards other publishers would have to apply for admission to the scheme. Any practising scientist *S* could apply for a passbook. This would contain a list of all ACRE journals and *S* would enter 1, 2, 3 (say) against a selection of these, and there would be space for him to enter details of his publications over the past 3 years (say). He would send his passbook to the publishers of his selected journal number 1 (*J1*) who would enter the maximum number of pages they would allocate to *S* for the

ensuing year. Publishers *J1* would forward the passbook to *J2* who would make their allocation in the knowledge of what *J1* had done; similarly for *J3*, who would then return the book to *S*. This operation would be repeated each year, or whatever would be found the most useful interval. Any young scientist, or scientist from abroad, or scientist entering a new field, being duly accredited, could be given a standard starting allocation of say five pages in any journal of his choice. In the course of 2 or 3 years he could then work himself into the situation of *S*.

The printing would be done according to a system now coming into use for some reports of symposia, and so on. The journals would supply the author with paper of standard form on which his work would have to be typed according to standard instructions. Each sheet would be photographically reproduced as a page of the journal, exactly as the author submits it. The author would then know automatically how he is using up his page allocation. If a paper is submitted by several authors, they would have to agree among themselves as to how many pages each would contribute from his own allocation, and inform the publishers accordingly.

The advantages to the scientific community generally would include the end of refereeing and editing other people's work, no correcting of printer's proofs, speedier publication and speedier production of offprints, an end to the production of preprints, and a reduction of costs all round. There would be other advantages to the publishers, such as more reliable estimation of the amount of material to be published within any given time.

If an author maintained a high standard, he would earn all the allocation he needs. If an author published bad or badly presented work, he would find his allocation greatly reduced. The discipline on authors would be wonderfully salutary!

The interesting problem would be the business of allocating pages. The publishers of a journal could prescribe a total number of pages for a year. Then they could ask a small panel drawn from the authors who had published most in that journal during a few previous years to allocate this total among the authors applying. The deliberations of the panel might be entertaining—more entertaining than refereeing papers.

Other people can doubtless suggest many improvements to the scheme, but in one form or another it might solve some of the many problems now besetting those who have the responsibility for seeing that scientific research is published as efficiently as possible.

Yours faithfully,

W. H. MCCREA

Astronomy Centre,
University of Sussex

Short RNA Chains

SIR,—It would be interesting to know whether the discovery mentioned by your Cell Biology Correspondent¹ that "short RNA chains can *in vitro* and may *in vivo* act as primers for the self replication of double and single stranded DNAs by DNA polymerases which elongate DNA chains in the 5'-3' direction, polymerizing deoxy nucleotide triphosphates onto 3' hydroxy groups of primers" is related to the finding made some years ago that small amounts of RNAase-resistant RNA seemed to be associated with DNA after the nucleic acids from HeLa cells² or mouse ascites sarcoma cells³ had been separated by chromatography or density gradient centrifugation.

Yours faithfully,

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¹Nature, 238, 247 (1972).

²Levis, A. G., Krsmanovic, V., and Errera, M., *Biochim. Biophys. Acta*, 145, 577 (1967).

³Watson, J. D., and Ralph, R. K., *Biochim. Biophys. Acta*, 138, 89 (1967).

Erratum

IN the article "New Antifertility Agent—an Orally Active Prostaglandin—ICI 74,205" by Anant P. Labhsetwar (*Nature*, 238, 400; 1972), the double bond in the upper side chain in ICI 74205 should have been shown in the *cis* and not the *trans* position in the structural formula on p. 401.

International Meetings

October 4, **Application of Finite Elements in Mechanical Engineering Design—A Survey of Current Practice**, London (Institution of Mechanical Engineers, 1 Birdcage Walk, London SW1H 9JJ).

October 12, **Recent Developments in Compact High Duty Heat Exchangers**, London (Institution of Mechanical Engineers, 1 Birdcage Walk, London SW1H 9JJ).

October 16–20, **National Society for Clean Air Conference**, Scarborough (National Society for Clean Air, 134–137 North Street, Brighton BN1 1RG).

October 24–26, **Site Testing of Pumps**, London (Institution of Mechanical Engineers, 1 Birdcage Walk, London SW1H 9JJ).

October 24–26, **The Car of the Future—The Practical Influence of Legislative and Economic Factors—Reliability—Easier Maintenance**, London (Institution of Mechanical Engineers, 1 Birdcage Walk, London SW1H 9JJ).

October 26, **A Study of the Fixation of Fractures using Plates: Clinical Complications of the Use of Such Devices and an Experimental Study of their Characteristics**, London (Institution of Mechanical Engineers, 1 Birdcage Walk, London SW1H 9JJ).

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